

PYODERMA GANGRENOSUM

THE GROOTE SCHUUR HOSPITAL EXPERIENCE

1970-1990

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Part III

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by

PAT LAWRENCE MBChB

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*Supervisor: Dr S Jessop MBChB, FFDerm (SA)
Department of Dermatology
Groote Schuur Hospital
University of Cape Town
Cape Town
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CHAPTER ONE

OBJECTIVES

1. To document the Groote Schuur Hospital experience of the incidence, clinical and laboratory features, associated systemic disorders and response to therapeutic regimens in patients with pyoderma gangrenosum seen at Groote Schuur Hospital between 1970 and 1990.
2. To compare the Groote Schuur experience with other reported series based on a literature review.
3. To formulate an appropriate protocol for the diagnostic evaluation and treatment of the patient presenting with pyoderma gangrenosum.

CHAPTER TWO

LITERATURE REVIEW

INTRODUCTION

The original article by Brunsting et al,¹ established pyoderma gangrenosum (PG) as a distinct clinical entity characterized by exacerbation and remissions of morphologically unique cutaneous ulcers. Although bacteria are not the cause, and gangrene almost never supervenes, the term *Pyoderma Gangrenosum* remains well entrenched in the medical literature.

PG is frequently thought to be a manifestation of an underlying systemic disease. In Brunsting's series of 1930¹, four of the patients suffered from ulcerative colitis and one had a chronic empyema. Subsequent reports^{2,3,4} emphasised the association with bowel disease although the list of a wide variety of other systemic diseases continues to grow. It has become increasingly apparent that PG is not limited to one systemic disease setting⁵.

In 20% to 30% of patients with PG, no associated disease process can be identified at the time the cutaneous lesions first appear^{2,3,4}. The diagnosis of PG still depends principally on the medical history and the clinical examination of the patient focussing specifically on the appearance of the cutaneous lesions and exclusion of other various disease processes⁶. No specific laboratory or histologic feature of this disease has been demonstrated. In fact, a diversity of associated disorders and laboratory abnormalities found in patients with PG has done little to elucidate its pathogenesis, and treatment remains empiric.

CLINICAL FEATURES

Little can be done to improve on the original description by Brunsting et al¹ of the skin lesions:

"The borders of the ulcer were well defined because of their striking blue color, which clearly outlined the lesion as it extended peripherally in rough serpiginous configuration. The blue zone consisted of an edematous, boggy strip from 5 to 8mm wide, in which there had been extensive undermining and necrosis of the subcutaneous tissue, the epidermis remaining as a thin, gray, translucent film extending over the crater of the lesion, in a ragged, irregular fashion (figure 1). Healing occurred by epithelial outgrowths from the periphery with resultant thin, atrophic scarring, with some brownish pigmentation (figure 2). The elementary lesions occurred in crops as small, discrete pustules surrounded by an inflammatory areola. Within a few days, the center of the pustule softened and the covering skin became blue and broke down (figure 3). The lesion either underwent involution or extended peripherally, to coalesce with others adjoining to form a larger, superficial ulcerative process, as described."

Figure 1 : "Classic" PG (case 4)



Figure 2 : Atrophic scarring and brown pigmentation of healed PG (case 27)



Figure 3 : Vesico-pustules and developing ulcers of early PG (case 27)



The lesions may appear anywhere on the body, including the mucous membranes, but are found most commonly on the legs⁷. They may be single or multiple, developing simultaneously or in sequence. Pain is a prominent feature and is sometimes so severe that narcotic analgesia is required. Local trauma or irritation is thought to incite some of the early lesions. In Perry's series³, 18 of the 62 patients with PG (25,8 percent) gave a history of preceding trauma at the site at which the PG developed. A similar percentage of patients in the largest series to date⁴, 23 of 86 (26,7 percent) patients, gave a history of a precipitating factor that varied from minor trauma to surgical procedures. Other reports emphasize the association of minor trauma or surgery in the development of PG⁸⁻¹⁰.

Pyoderma gangrenosum may affect patients in any age group. It has been described in patients from the first decade^{11,12} to the ninth decades of life^{13,14}. However, most of the patients reported, developed their PG between 25 and 45 years of age⁴.

The natural history of this disorder follows one of two patterns^{15,16}:

- (1) **ACUTE, RAPIDLY PROGRESSIVE**, in which the ulcers enlarge dramatically during a period of days, unless arrested by systemic treatment.
- (2) **CHRONIC, SLOWLY PROGRESSIVE**, where the ulcers slowly enlarge during a period of weeks to months. Systemic therapy is not always indicated if adequate facilities are available for good local therapy.

CLINICAL VARIANTS OF PG

MALIGNANT PYODERMA OR PYODERMA GANGRENOSUM OF HEAD AND NECK

The clinical entity of malignant pyoderma (MP) was first described by Perry et al in 1968¹⁷, who regarded it as distinct from the accepted description of pyoderma gangrenosum, for the following reasons :

- (a) The atypical location of the lesions (predominantly on the head and neck)
- (b) The absence of undermined borders and erythema around the ulcers (figure 4).

Figure 4 : Atypical PG of head and neck (case 5)



However, since that publication, subsequent reports^{18,19} have challenged the supposition that MP or PG of the head and neck (except for its site) is different from pyoderma gangrenosum elsewhere on the body. As far back as 1931, a 28 year old woman with known chronic ulcerative colitis was described as having severe pustular and ulcerative lesions confined to the face and neck and a diagnosis of pyoderma gangrenosum was made²⁰.

Further reports²¹⁻²⁴ support the contention that PG and MP are probably identical disorders since many of the lesions, despite the location on head or neck, had the typical blue undermined border of classic PG, were often associated with an underlying disorder and responded like Perry's "malignant pyodermas" to systemic corticosteroids. Most dermatologists also believe that the term malignant to describe this form of pyoderma is inappropriate¹⁸.

BULLOUS PG OR ATYPICAL PG

This variant was first described by Perry and Winkelmann in 1972²⁵. They reported 3 patients who developed unusual skin lesions that were suggestive of pyoderma gangrenosum but were more superficial, less destructive of tissue and had concentric bullous inflammatory areas of involvement spreading centrifugally throughout the lesions. The borders of the lesions had a more subdued blue-gray appearance as opposed to the striking deeply purple colour of the more typical PG lesions. All 3 patients, on investigation were found to be suffering from leukaemia. They concluded that the skin lesions were an atypical form of PG by excluding leukaemic infiltrates and known causes of pyodermatous skin lesions.

Since this report, the association of atypical PG with leukaemia and pre-leukaemic conditions has been well established²⁶⁻³². The course of the skin lesions may, but does not always,

parallel the course of the underlying disease. Healing occurs with a more superficial scar than is seen in typical PG.

ORAL PYODERMA GANGRENOSUM

Reports of PG involving the oral cavity are rare. Basu et al³³ reported 2 out of 100 patients with inflammatory bowel disease (IBD) who had oral mucosal lesions analagous to PG. These lesions were described as irregular shaped ulcers, 15 to 20mm diameter, with rolled out margins and a greyish-coloured base. The ulcers were painful and developed over a period of four to eight weeks during a stage when bowel symptoms were present and laboratory tests suggested considerable activity. The majority of the reports of oral PG³³⁻³⁶, have been described in association with inflammatory bowel disease (IBD). There have been two published reports of oral PG where evidence of underlying systemic disease was lacking^{37,38}. In every case thus far, the oral lesions were accompanied by cutaneous ulcers.

PYOSTOMATITIS VEGETANS

Pyostomatitis vegetans is a rare and unusual disorder of the oral cavity, characterized by erythema and oedema of the mucosa, studded by numerous small superficial yellow pustules. Its significance lies in its association with IBD, either ulcerative colitis or Crohn's disease³⁹.

Callen⁷ suggests that pyostomatitis vegetans is a potential variant of PG based on its strong association with IBD, repeatedly negative cultures of the oral abscesses and pustules for bacteria, viruses and fungi and associated ulcerative and vegetative skin lesions, which in some patients resembled classic pyoderma gangrenosum. Mc Carthy, on the other hand, who first coined the term pyostomatitis vegetans in 1949³⁹ and other reporters⁴⁰⁻⁴², regard

this entity as a specific marker for inflammatory bowel disease, rather than oral PG. The lesions are uniformly responsive to systemic corticosteroids.

PUSTULAR ERUPTION OF ULCERATIVE COLITIS

Some authors regard this as a variant of pyoderma gangrenosum as some of the pustular lesions in this group of patients were seen to progress to more typical lesions of PG⁴³⁻⁴⁵.

O'Loughlin and Perry⁴⁴ were probably responsible for the first description of this entity. The initial lesions were multiple, small, 1 to 3mm pustules on an erythematous base, widely scattered over many surfaces on the body. They differed from pustular psoriasis in that they did not occur in sheets. Callen and Woo⁴³ described a patient in whom hundreds of pustules developed and yet only three resulted in typical ulceration of PG. The pustules were sterile when cultured. All of the reported patients with this variant had ulcerative colitis. Like classic PG, the course of the skin lesions did not necessarily parallel the course of the underlying disease⁴⁴.

SUPERFICIAL GRANULOMATOUS PYODERMA : A LOCALIZED VEGETATIVE FORM OF PYODERMA GANGRENOSUM.

Wilson-Jones and Winkelmann described this form of pyoderma gangrenosum in 1988⁴⁶. In this report, twenty five patients who presented with chronic superficial ulcerative pyoderma were considered clinically, by experienced clinicians, to be suffering from pyoderma gangrenosum. The characteristic indolent lesions with sinuses, vegetative or crusted borders, and cribriform scars were often single and recurrent. The back was the most common location of the lesions (figure 5). The recurrence and spread of individual lesions with the absence of an infectious cause, suggested the diagnosis of pyoderma gangrenosum, as did the

presence of multiple lesions in a few cases. The superficial nature of the ulcers and the lack of liquefying, rapidly advancing borders were different from classic pyoderma gangrenosum.

The histopathologic pattern in these cases were distinct and of a granulomatous nature with superficial, focal abscesses surrounded by histiocytes and foreign body giant cells.

The lesions frequently healed without corticosteroid therapy or even spontaneously. Wilson-Jones and Winkelmann believe that they have described a unique clinico-pathological entity, which is perhaps a limited form of pyoderma gangrenosum, the recognition of which offers an opportunity for a conservative medical approach. (In their series of 25 patients, healing occurred without systemic corticosteroid treatment in all but 3 patients). Follow-up showed that the lesions healed within a short time after the initiation of consistent therapy. The majority of these patients (21 of 25) demonstrated no underlying systemic disease.

Figure 5 : Localised, vegetative form of PG (case 40)



UNUSUAL SITES FOR PYODERMA GANGRENOSUM

Special mention is made of the following sites where pyoderma gangrenosum may not be readily recognized and thus be misdiagnosed.

PARASTOMAL PYODERMA GANGRENOSUM

The occurrence of PG around the stomal sites was first brought to notice by Mc Garity et al in 1984⁴⁷. They suggested that parastomal pyoderma gangrenosum may be under-reported because of a general unfamiliarity with this lesion and the difficulty in distinguishing it from other parastomal skin lesions, such as parastomal dermatitis, fistulas from recurrent Crohn's disease, abscesses from suture reaction or wound contamination, pyogenic skin infections, Meleney's ulcer, deep or intermittent mycotic infection, necrotizing vasculitis and factitial ulcerations. In their cases, the parastomal PG showed wide variability in time of appearance relative to first surgery for Crohn's disease, disease course, response to medical therapy, and relationship to underlying disease. The optimal medical treatment of parastomal pyoderma gangrenosum appeared to be corticosteroids combined with local wound care. If this regimen failed, revision and/or relocation of the ileostomy appeared to give good results. Parastomal PG may be commoner in patients with Crohn's disease than is generally believed⁴⁸.

GENITAL REGION

Involvement of the genital region by pyoderma gangrenosum is rare. The appearance and course may in no way differ from pyoderma gangrenosum elsewhere on the cutaneous surface, but special problems may arise with regard to perineal support, grafting and patient emotional response^{49,50}. In the reports referred to, both patients required extensive de-

bridement and grafting with adequate systemic corticosteroid cover before healing occurred. Strong psychological and emotional support played a major role in management.

PG of the penile and scrotal skin was the presenting feature of underlying inflammatory bowel disease in a patient reported by Sanusi et al⁵¹.

Maule et al⁵² recommend that in patients with IBD and perianal ulceration, peri-anal PG should always be excluded. Hughes et al⁵³, whose report on anal Crohn's disease prompted Maule's recommendation, agreed that similarities between peri-anal PG and the cavitating ulcers seen in Crohn's disease do exist, but that the latter were distinct from PG for the following reasons: first, the cavitating ulcers described in Crohn's disease were all at the level of the ano-rectal ring; second, the anal lesions tend to progress more slowly (in contrast to PG, which tends to be rapidly progressive); third, the ulcers in PG tend to respond to a short sharp course of high-dose oral steroid therapy, whereas in their experience, the cavitating ulcers in anal Crohn's disease do not. Fourth, PG is a relatively uncommon complication of Crohn's disease occurring in only 0.8% of a series of 961 patients described by Schoetz et al⁵⁴, whereas the cavitating ulcer is more common, and is one of the distinctive clinicopathological features of Crohn's disease.

HISTOPATHOLOGY

The histopathology of PG is not specific but is helpful in that the physician can rule out other disorders that may clinically appear as cutaneous ulceration⁷.

Su et al⁵⁵ studied the largest group of patients with PG (63 biopsy specimens) and found 3 patterns of histologic changes, depending on the site of biopsy:

- (a) If the biopsy was obtained from the erythematous zone peripheral to the ulcer, the histologic features were those of a lymphocytic vasculitis (endothelial swelling, fibrinoid necrosis, thrombosis, extravasation of erythrocytes and predominance of lymphocytes.)
- (b) If the necrotic, undermined edge of the ulcer was biopsied, a mixed cellular infiltrate of lymphocytes and neutrophils, lymphocytic vasculitis or perivascular inflammatory infiltration and early abscess formation were usually present.
- (c) If the specimen was taken from the ulcer floor, abscess formation and necrosis were apparent (non-specific necrotic findings)

They found that the level of involvement in the cutaneous biopsy specimens of pyoderma gangrenosum was usually deep. The majority showed involvement of panniculus as well as dermis (papillary and reticular).

Although biopsy specimens taken from lesions of PG in the vast majority of patients lack the histologic appearance of necrotizing vasculitis^{2,13,56}, a few exceptions have been described^{57,58,59}. The latter authors suggested that the histologic picture in their patients provided sufficient evidence for the vasculitic origin of PG. Callen maintains that neither leucocytoclastic vasculitis nor granuloma formation is part of the picture of PG⁷.

The association of atypical bullous PG and Sweets syndrome (SS) with myeloproliferative disorders has been noted⁶⁰. Both may be classified as neutrophilic dermatoses since they exhibit intense dermal inflammatory infiltrates composed of neutrophils with no histologic evidence of primary necrotizing vasculitis. There is obvious overlap between these two categories but the pathophysiologic mechanisms remain unknown. Some investigators have suggested that the inflammatory lesions of myeloproliferative disorders form a continuum

along a dynamic neutrophil-mediated process, ranging from classic SS to classic PG^{61,62}. Lending further support that PG is a neutrophil mediated process is its development in lesions of subcorneal pustular dermatosis⁶³.

AETIOLOGY AND PATHOGENESIS

The causative mechanism of PG is unknown. Although there are a set of recognized systemic disorders that are associated with PG, there has not been anything found in these conditions that sheds light on the underlying mechanisms of disease formation⁷. It is well established that infectious agents are not primarily involved. Repeated attempts at culturing early non-ulcerated lesions have failed to demonstrate viruses, fungi or bacteria.

Although the exact mechanisms are uncertain, there is a belief that development of PG is related to a defective immune system^{13,64,65}. Lazarus et al described four patients with cutaneous anergy and a lack of association between in vitro macrophage inhibition factor production and antigen-induced incorporation of tritiated thymidine in cultured lymphocytes¹³. Failure of normal delayed response to DNCB, candida and streptokinase has also been demonstrated⁶⁵. By this interpretation, lesions would occur when paralysis of the reticulo endothelial system is unable to protect the tissues from the effect of minimal injury. New lesions can be provoked by skin pricks as in Behcet's syndrome, with which there is some overlap⁶⁶. Such hyperactivity is greatest in the acute phase of the disease and near to existing lesions.

It is possible that in some patients, a factor in serum inhibits in-vivo function of the lymphocyte. Lymphocytes from several patients with PG have failed to produce macrophage inhibi-

tory factor (MIF), and serum from one patient was unable to suppress the mixed lymphocyte reaction⁶⁷.

A serum dermonecrotic factor causing necrosis of guinea pig skin has been demonstrated but its specificity is doubtful⁶⁵.

Tests of polymorphonuclear leucocyte function have demonstrated defects in phagocytosis, chemotaxis, random migration and the ability to kill staphylococci⁶⁸⁻⁷⁰.

The most compelling evidence of a defective immune mechanism lies in the increasing number of reports of PG associated with gammopathies⁷¹, and other disorders of the reticulo-endothelial system, such as T-cell imbalances⁷².

The role of immunoreactants in PG is unknown. Su et al noted deposits of IgG, IgA, IgM, C3 and fibrin in the papillary and reticular dermal vessels in 55 percent specimens studied, for which they had no valid explanation⁵⁵. It was unlikely that they originated as circulating immune complexes in view of the multitude of reports failing to demonstrate circulating immune complexes⁷.

A wide range of serological and biochemical tests have failed to reveal any significant or consistent abnormalities which may give insight into the pathogenesis of this unusual disorder⁷³.

Callen proposes that patients with PG have at least a partial defect in cell mediated immunity with an accompanying disturbance of polymorphonuclear leucocyte function and in such a predisposed individual, an inciting event, such as minor trauma, results in an abnormal response, manifested as the clinical lesion of PG⁷.

ASSOCIATED DISEASES

PG has been reported with a wide range of inflammatory, neoplastic and auto-immune disorders (Table 1)⁷.

TABLE 1 : DISEASES ASSOCIATED WITH PYODERMA GANGRENOSUM

Common Associations

Inflammatory bowel disease (IBD)

Chronic ulcerative colitis (CUC)

Regional enteritis, granulomatous colitis (Crohn's disease)

Rheumatic diseases

Seronegative with IBD

Seronegative without IBD

Rheumatoid arthritis

Spondylitis

Osteoarthritis

Hematologic diseases

Myelocytic leukemias

Hairy cell leukemia

Myelofibrosis, agnogenic myeloid metaplasia

Monoclonal gammopathy (IgA)

Rarely Reported Associations

Chronic active hepatitis

Myeloma

Polycythemia rubra vera

Paroxysmal nocturnal hemoglobinuria

Takayasu's arteritis

Primary biliary cirrhosis

Systemic lupus erythematosus

Wegener's granulomatosis

Hidradenitis suppurativa

Acne conglobata

Malignancy

Thyroid disease

Pulmonary disease

Sarcoidosis

Diabetes mellitus

Other pustular dermatosis

Endometriosis

Behcet's

AIDS

Inflammatory bowel disease still appears to be the most frequently reported association^{2,3,4,74,75} since Brunsting et al reported their series where 4 of the 5 patients had ulcerative colitis³. However, Hickman and Lazarus in a reappraisal found that this association was not as common as formerly suggested⁷⁶. The other common associations are arthritis, haematologic diseases and paraproteinaemias (particularly IgA).

ULCERATIVE COLITIS

The incidence of chronic ulcerative colitis (CUC) with PG has varied from 13 percent (2 of 15 patients) reported by Holt et al¹⁵, to 50 percent (31 of 62 patients) in a series reported by Perry³. In the latter study, 25 patients had the colitis prior to the onset of the skin lesions; in 2, the bowel and skin disease began at the same time, and in the remaining 4, the CUC was discovered as a result of evaluation of the skin. In a study of patients with PG and CUC from Cleveland Clinic⁷⁵ only 3 of 21 patients (14 percent) presented with PG prior to the recognition of ulcerative colitis. The majority of patients had active CUC at the time of diagnosis⁷⁵.

Several authors have suggested that PG occurs in patients with severe attacks of colitis⁷⁷ while others found no relationship between severity and extent of CUC and the appearance of PG⁷⁵.

The true frequency of CUC in patients with PG is probably around 10 percent, and the relationship of the activity of the skin disease to activity of the bowel disease is not consistent⁷. The speculation that PG in CUC is a result of immunological reaction to bacterial and dietary antigens absorbed through damaged colonic mucosa remains unproven.

CROHN'S DISEASE

The frequency of Crohn's disease (regional enteritis) with PG varies from series to series, but is generally low. In Perry's group of 62 patients³, not a single patient had Crohn's disease, while in the Mayo clinic experience⁴, 14 of 86 patients (16,3 percent) had Crohn's. In the most recent of published series, Prystowsky et al found 2 of 21 patients (9,5 percent), suffering from Crohn's⁷⁸. Not only is the frequency of Crohn's disease in patients with PG low, but in Crohn's patients, PG is rare. This conclusion was reached by Schoetz et al who studied a group of 961 patients with Crohn's disease and found PG in only 8 patients (0,8 percent)⁵⁴.

The relationship of the activity of the bowel disease to the activity of the skin-disease has not been well studied. In Schoetz's group, all 8 patients developed their PG during an active phase of the disease⁵⁴. In two, the PG developed coincidentally with the onset of bowel symptoms, while the remaining 6 developed their skin lesions on an average of 7.3 years after developing Crohn's disease. They found that the most important part of treating the PG was controlling the underlying disease (a combination of surgery, systemic corticosteroids and sulfasalazine were usually employed). On the other hand, radical surgery to eradicate the bowel disease does not necessarily preclude the development of PG thereafter⁷⁵.

ARTHRITIS

Joint disease is a common occurrence in patients with PG. Holt et al found 8 of 15 patients with PG who had an associated polyarthritis⁵⁶. His was the first study to take a careful look at the pattern of arthritis in PG and he found that 4 of the 8 had a progressive, erosive, symmetrical seronegative polyarthritis which appeared to be peculiar to PG. He felt that this form of arthritis was unlikely to be a manifestation of inflammatory bowel disease (IBD)

since three of the four patients showed no evidence of bowel disease. In addition, "colitic" arthritis is described as a distinctive, acute, oligo-articular, asymmetrical intermittent inflammatory disease, usually affecting large joints, does not progress to joint destruction and whose activity is closely related to the activity of the underlying bowel disease⁷⁹. The fourth patient, although having ulcerative colitis, again manifested a polyarthritis, unlike colitic arthritis i.e. it preceded the onset of bowel symptoms, was never punctuated by acute episodes, was not related to exacerbations of colitis, and was associated with x-ray evidence of para-articular bone bridging seen more typically in other sero-negative spondyloarthropathies. The course of the arthritis in these 4 patients was progressive with development of disabling joint deformities and erosive destruction of joints despite treatment with penicillamine, corticosteroids and non-steroidal anti-inflammatory drugs.

Of the remaining 4 patients, 2 had seropositive, erosive rheumatoid arthritis, 1 had seronegative polyarthritis with ulcerative proctitis and 1 had seronegative polyarthritis with chondrocalcinosis.

Powell et al also found that arthritis was the most frequent associated disorder (32 of 86 patients) in his series⁴. Of these, 13 had seronegative arthritis with IBD and 9 seronegative arthritis without IBD. Of the remaining patients, 4 had classic seropositive rheumatoid arthritis, 3 had ankylosing spondylitis and 3 had osteoarthritis.

In the case of classic rheumatoid arthritis, it is often unclear whether the more appropriate diagnosis might be rheumatoid vasculitic ulcers rather than PG but, more often than not, a leucocytoclastic vasculitis is not found on skin biopsy^{7,15}.

In those patients, with a seronegative rheumatoid-like arthritis that is not associated with inflammatory bowel disease, the arthritis seems to follow the same course as the PG⁷.

In Perry's series of 62 patients scant attention was paid to the presence or absence of arthritis³.

Although a few patients with PG exhibit seropositive rheumatoid arthritis⁸⁰, the majority of patients show negative findings on serologic examination⁵.

The relationship between arthritis and PG is difficult to sort out, particularly since inflammatory bowel disease and pyoderma gangrenosum each have their own arthritic components⁶.

HAEMATOLOGICAL MALIGNANCY

An atypical form of PG (a superficial, bullous variety) is usually reported in association with leukaemia and pre-leukaemic syndromes²⁵⁻³². However, the more typical PG ulcers have been reported as well^{26,81}. Usually, the PG post-dates the development of the haematological disorder, but may be the presenting sign^{82,83}.

Recurrence of skin lesions may herald a relapse of the leukaemia in a patient in remission²⁷. Most frequently, the leukaemia has been of the myelocytic series usually an acute myelomonocytic leukaemia⁷, although the number of reports in association with the preleukaemic state of myelofibrosis and myelodysplasia is increasing^{29,84,85,86}.

Treatment of the haematological disease may lead to remission of the skin lesions although the presence of PG usually indicates severe disease^{25,27}.

MONOCLONAL GAMMOPATHY AND MYELOMA

The reported incidence of monoclonal gammopathies associated with PG has varied between 10 and 20%^{4,56,78}. Usually the gammopathy was IgA^{71,87}. Only rarely does the patient with a benign monoclonal gammopathy and PG progress to develop myeloma⁷¹.

Several patients with multiple myeloma have also been reported⁸⁸, but this occurrence is much less frequent than the association with benign monoclonal gammopathy⁷⁸. Although the importance of the association of paraproteinaemia with PG remains unclear, patients with a gammopathy should be followed carefully for the rare development of myeloma⁷¹.

INTERNAL MALIGNANCIES

Other than the established association of PG and leukaemias, the association of internal malignancies and PG is rare. The isolated reports suggest that the malignancy and the PG were probably coincidental, except for one report, where resection of an adrenocortical carcinoma in a patient with PG and long-standing ulcerative colitis, led to the complete clearing of the previously troublesome PG⁸⁹.

LESS COMMON DISEASE ASSOCIATIONS

The list of uncommon disease associations with PG continues to grow (Table 1). The numbers of these miscellaneous disorders, however, are too small to draw any conclusions. The exception may be large vessel vasculitis (Takayasu's disease) where a third of Japanese patients with this disease are reported to have coexisting PG⁹⁰.

Chronic active hepatitis⁹¹, systemic lupus erythematosus⁹² and sarcoidosis⁹³ are some of the rarer conditions linked to PG. More recently, human immunodeficiency virus infection and PG has been reported in two children⁹⁴.

DIFFERENTIAL DIAGNOSIS

An important part of the evaluation of a patient with PG is to rule out other causes of cutaneous ulceration. This is particularly important in those patients who fail to respond to what is considered adequate treatment for PG.

The following should be excluded :

- (1) Infectious diseases such as tuberculosis (Callen had a patient sent from another centre with a diagnosis of PG who was found to have tuberculosis)⁷, deep fungal infections (sporotrichosis masquerading as pyoderma gangrenosum is reported)⁹⁵, bacterial (a leg ulcer of the PG type was in fact a manifestation of tertiary cutaneous syphilis)⁹⁶, viral infections, and in the setting of acquired immunodeficiency syndrome (AIDS)⁹⁷, bizarre organisms.
- (2) Halogenodermas
- (3) Vasculitis (Wegener's granulomatosis presented as PG)⁹⁸
- (4) Venous or arterial insufficiency
- (5) Neoplasms (Histiocytosis X mimicking pyoderma gangrenosum is reported in an adult)⁹⁹
- (6) Drug eruptions¹⁰⁰
- (7) Factitial ulcerations.
- (8) Chronic granulomatous disease¹⁰¹.

PROGNOSIS

This is most predictable in those patients in whom an identifiable disease is recognizable and amenable to treatment. But even here, the prognosis is that of the associated disease and this may be unfavourable, especially if the reticulo-endothelial system is involved. However, with ulcerative colitis and Crohn's disease, control of the internal condition can be expected to resolve the skin problem, although there are always exceptions^{54,75,102,103}.

TREATMENT

It is difficult to evaluate the treatment of a condition in which pathogenesis is unknown, the disease course unpredictable (with spontaneous remissions), and where disease activity may be related to an associated underlying disorder¹⁶. As a result of these factors, the therapeutic manoeuvres take on the form of an art in medicine. Recognition of underlying disease amenable to treatment is important. PG in patients with leukaemia, especially of the acute type, has improved or cleared completely after chemotherapy^{25,27}. Similarly, patients with PG and CAH have experienced dramatic clearing of their skin lesions when the hepatitis was treated with immunosuppressive agents⁹¹. In patients with CUC, skin lesions may respond to bowel resection, where oral therapy has failed⁷⁴. However, there are patients in whom total colectomy, including removal of the recto-sigmoid colon, failed to result in remission¹⁰², or where PG occurred years after bowel surgery¹⁰³. It is, therefore, important to have the proper bowel indications for this aggressive approach.

LOCAL THERAPY, regardless of the presence or absence of underlying associated disease, is important, since patients have been known to recover with topical treatment alone^{4,46}. In a disease characterized by pathergy, aggressive debridement should be avoided. Skin grafting should be avoided, if possible, but in cases of perineal involve-

ment^{49,50}, it is often unavoidable. Hyperbaric oxygen preparation of skin prior to grafting PG is recommended, as it is claimed to promote healing¹⁰⁴.

Other local measures include dressings,⁴⁸ elevation, rest, topical agents like sodium cromoglycate¹⁰⁵ and intralesional steroids¹⁰⁶.

Cleansing with antibacterial agents such as hydrogen peroxide or benzoyl peroxide have been reported to be beneficial in an occasional patient¹⁰⁷.

For those patients, not responding to local treatment, or in whom progression of the disease is dramatic and for patients with recurrent disease, systemic therapy is indicated.

SULFASALAZINE, in doses of 4g/day was the first widely and successfully used drug in the treatment of PG². It had been used by gastroenterologists for treatment of ulcerative colitis, with good results, and, since pyoderma gangrenosum may parallel the course of intestinal disease, it seemed reasonable to administer it for the treatment of the skin disease. It has been found to benefit patients with PG without IBD².

SULFAPYRIDINE, (which together with aminosalicic acid is formed by the splitting of sulfasalazine by gut bacteria) has also been shown to be beneficial in those PG patients who have a dermatitis herpetiformis-like eruption². In doses of up to 4g/day, it proved an effective treatment^{4,108}. It was apparent that sulfasalazine and sulfapyridine were not acting primarily as antibacterial agents in pyoderma gangrenosum, since other antibiotics were usually ineffective, and maintenance therapy often used doses too low to induce optimal antimicrobial effects¹⁶. Since the spectrum of diseases responding to sulfapyridine therapy is similar to that responding to sulfone therapy, sulfones were also administered, (usually diaminodiphenylsulfone, in doses up to 400mg/day), and found to be beneficial in the treat-

ment of pyoderma gangrenosum¹⁰⁸. The anti-inflammatory effects of the sulfones may be related to their severe inhibition of the myeloperoxidase-H₂O₂-halide mediated cytotoxic system in polymorphonuclear leucocytes¹⁰⁹ an accumulation of which characterizes PG lesions. Newell et al believe that sulfones are the drugs of choice in treatment of pyoderma gangrenosum, especially for the chronic, slowly progressive form of disease¹⁶. Treatment failures are thought to be the result of inadequate dosage. Disease resistant to sulfapyridine therapy may respond to sulfones and vice versa¹⁰⁶.

ADRENAL STEROIDS have been administered systemically for pyoderma gangrenosum for over 30 years¹¹⁰ and have become the most extensively used form of treatment. They are unquestionably effective and are considered by many to be the drug of choice for the acute, rapidly progressive form of the disorder⁵⁶. Large oral doses of prednisone (40 to 120mg/day) are usually required to arrest the disease. The successful use of pulse corticosteroid therapy in three patients with severe and/or recurrent disease¹¹¹ and in combination with dapsone¹¹² has been reported. The potential for cardiac arrhythmias and death as a result of electrolyte abnormalities mandates that pulse therapy be administered in a hospital setting with the appropriate monitoring. Pulse therapy refers to the use of suprapharmacologic doses of corticosteroids (patients are infused with IG methylprednisolone in 150ml of 5% dextrose between 8 - 9am daily for three to five days). The pulse therapy is then followed by maintenance therapy with oral prednisone combined with steroid sparing agents like sulfasalazine, dapsone or sulfapyridine⁷⁸. Prolonged maintenance therapy with oral adrenal steroids, even at relatively low dosage levels, may be associated with serious side effects. In one review, four patients died of what the authors termed "adrenal steroid - induced complications"⁷⁶.

CLOFAZAMINE, a phendimetrazine tartrate derivative previously used for its anti-microbial effect against mycobacteria, has been found to be effective in the treatment of PG¹¹³⁻¹¹⁵. The usual dose was 300mg/day. The mechanism of drug action is unknown.

Clofazamine is known to enhance neutrophil phagocytosis and intracellular bacterial killing and stimulates macrophage activity, but few of the patients treated had demonstrable defects in neutrophil or macrophage function^{113,115}. Other antimicrobial agents found to be successful in some cases of PG are minocycline hydrochloride¹¹⁶⁻¹¹⁸ and rifampin²⁶. Minocycline may be effective in part because of the anti-inflammatory and antichemotactic properties of the tetracycline, and presumably tetracycline derived drugs¹⁶.

IMMUNOSUPPRESSIVE THERAPY is another less common but well described treatment administered for systemic effects and is generally reserved for severe disease. Immunosuppressive drugs have occasionally been used in combination with adrenal steroids, but in a small number of cases, these agents have been given as the sole form of treatment¹⁶. Azathioprine in dosages of 100 to 150mg/day, has been the most frequently used drug, and although it has not been universally beneficial⁵⁶, it has been effective in patients with^{91,92} and without associated underlying disease¹⁶. Cyclophosphamide has been rarely used but in one young patient with severe unresponsive PG, its use resulted in dramatic clearing of the skin lesions¹¹⁹. Encouraging responses were also obtained with the use of cyclosporin A in several patients with recalcitrant pyoderma gangrenosum¹²⁰⁻¹²².

Other miscellaneous treatments used have included plasmapheresis¹²³, and thalidomide^{65,124}. Radiation therapy and electron beam irradiation have been attempted with little success¹²⁵. Systemic antibiotics may be needed for troublesome secondary infection which is inevitably present in skin lesions of pyoderma gangrenosum. Treatment, although frequently effective, remains empiric. There is no single agent that is effective in all patients in

whom it is used. Toxicity and undesirable side effects of the agents used are common. Finally, the need to be certain that the ulceration is not due to some other treatable cause, particularly infections, cannot be overstressed⁷.

CHAPTER THREE

MATERIALS AND METHODS

The records of patients diagnosed as having pyoderma gangrenosum at Groote Schuur Hospital, Cape Town, between 1970 and 1990 were obtained from the department of Informatics, Dermatology and Pathology at this institution and then reviewed (See Appendix). The patients' age at onset, the presence of precipitating factors, site of first lesion, duration of first course, recurrences, intervals of healing, therapy, response to treatment and follow-up periods were recorded. The histology reports and microscopic slides of those patients that were biopsied were obtained from the departments of Dermatology and Pathology. The histology was reviewed with a consultant pathologist. Results of special tests, including serum protein electrophoresis and delayed hypersensitivity skin tests, were also reviewed. Informed consent was obtained from those patients where identification was possible from photographs appearing in this publication.

CHAPTER FOUR

RESULTS

Pyoderma gangrenosum was diagnosed in 45 patients seen at Groote Schuur hospital between 1970 and 1990. In 41 patients, the diagnosis was made or confirmed by dermatologists in the department of dermatology, 2 (who had parastomal PG) were diagnosed by an experienced stomatherapy nursing sister, and 2 were diagnosed by physicians in the haematology department.

CLINICAL FEATURES

In 41 patients (91.1%), the diagnosis in the active phase was based on the clinical features of progressively enlarging ulcers with violaceous undermined borders, surrounded by a zone of erythema.

Of the remaining 4, 2 (cases 33,34) were atypical PG of the head and neck (figures 6 and 7), 1 (case 20) was the bullous variant of PG associated with a pre-leukaemic state (figure 8), while the fourth (figure 5, case 40) was classified as the localised vegetative variant described by Wilson-Jones⁴⁵. Oral involvement was documented in 4 patients (cases 1, 9, 26, 39).

Figure 6 : Atypical PG of head and neck (case 33)



Figure 7 : Atypical PG of head and neck in a child (case 34)



Figure 8 : Atypical bullous PG (case 20)

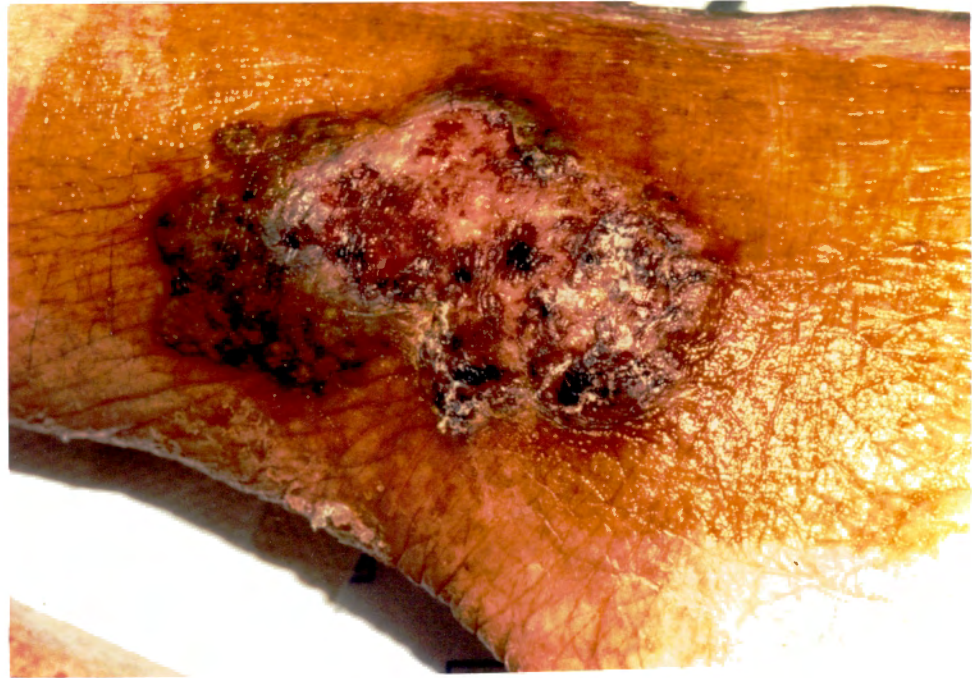
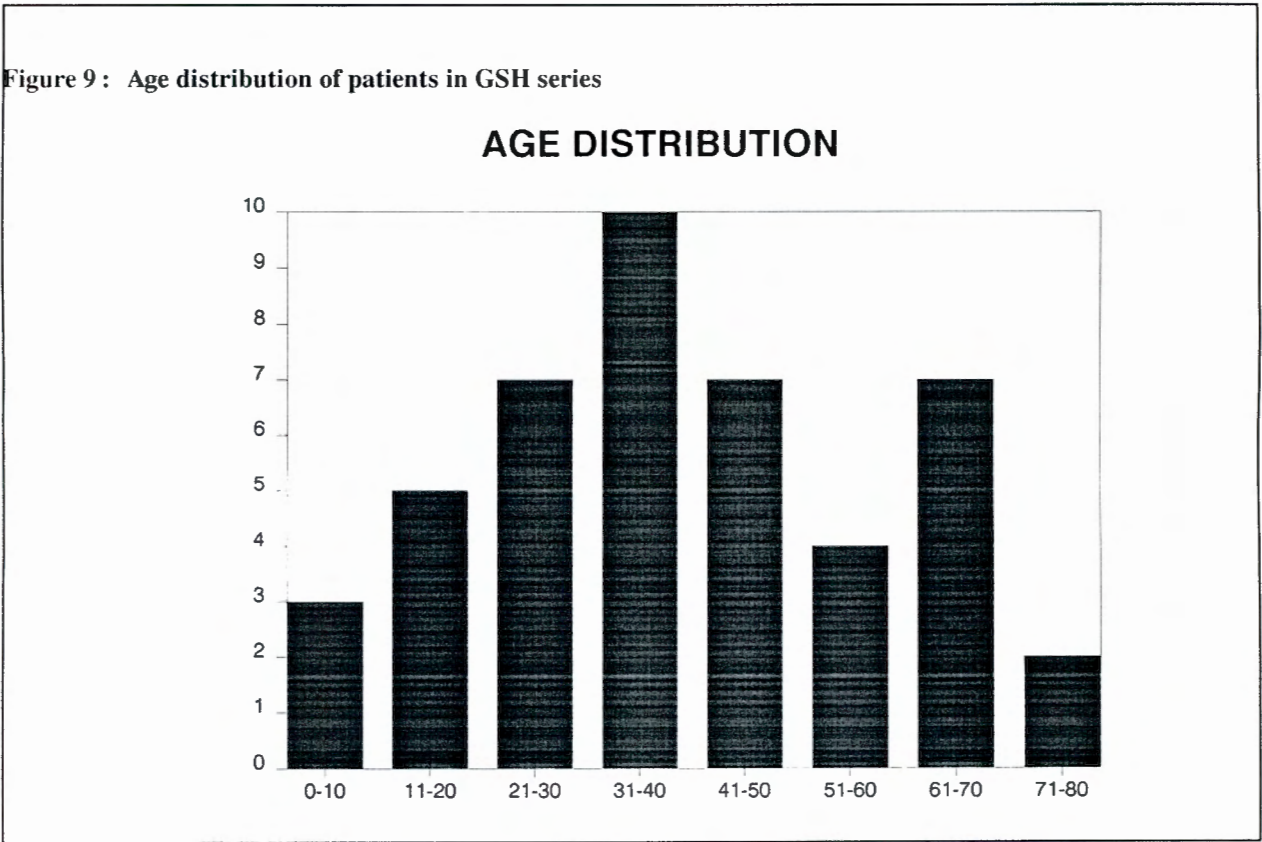


Figure 9 : Age distribution of patients in GSH series



In this study, 26 patients (57.8%) were female and 19 (42.2%) were male. The age of onset ranged from 8 to 72 years, with most patients developing their disease from the second through to the sixth decade (figure 9). Four patients (8.9%) developed pyoderma gangrenosum in childhood, that is on or before the age of 14 years (cases 26, 34, 39, 41).

The initial lesions of PG occurred at various sites (table 2). The lower limbs were the most frequently affected; 34 patients had lesions in this area, and 15 of the 34 had no other cutaneous involvement. Five patients (cases 2, 7, 8, 13, 14) had parastomal involvement (eg. figures 10 and 11), three, head and neck, two truncal, and one had the initial lesion involving the oral mucosa.

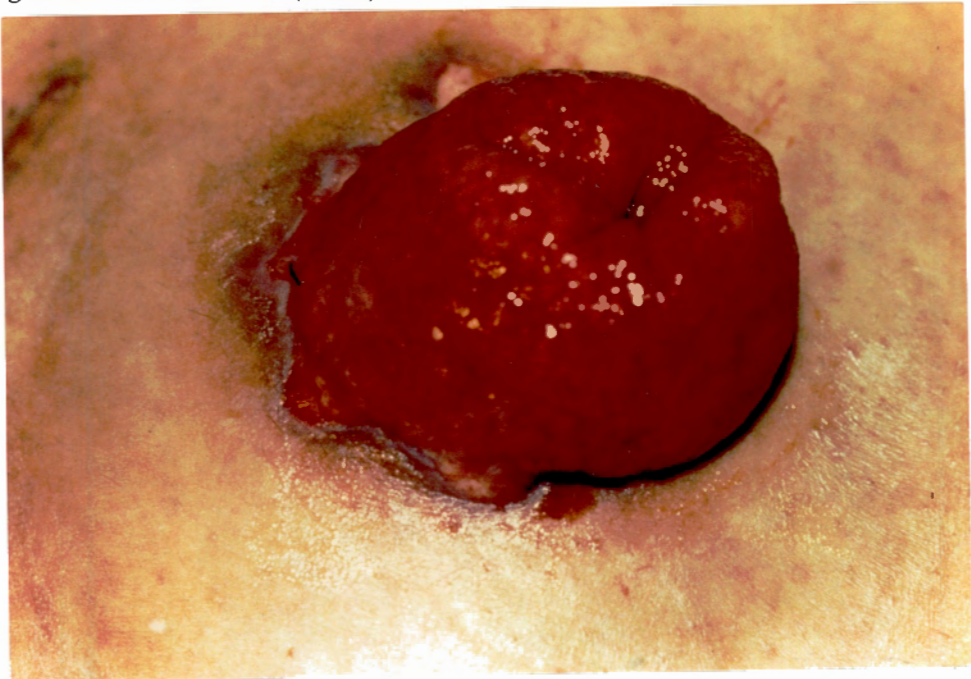
TABLE 2 : SITE OF FIRST LESION

LOWER LIMB :	:	34
HEAD & NECK	:	3
PARASTOMAL	:	5
TRUNK	:	2
ORAL MUCOSA	:	1

Figure 10 : Parastomal PG (case 2)



Figure 11 : Parastomal PG (case 8)



Three patients (cases 2,10,28), in addition to lesions elsewhere, had severe perineal involvement (eg. Figure 12).

Figure 12 : Perineal PG (case 2)



Pain in the lesions was a major feature in 35 patients. Twelve patients (28.6 percent) gave a history of a precipitating factor that varied from minor trauma to surgical procedures.

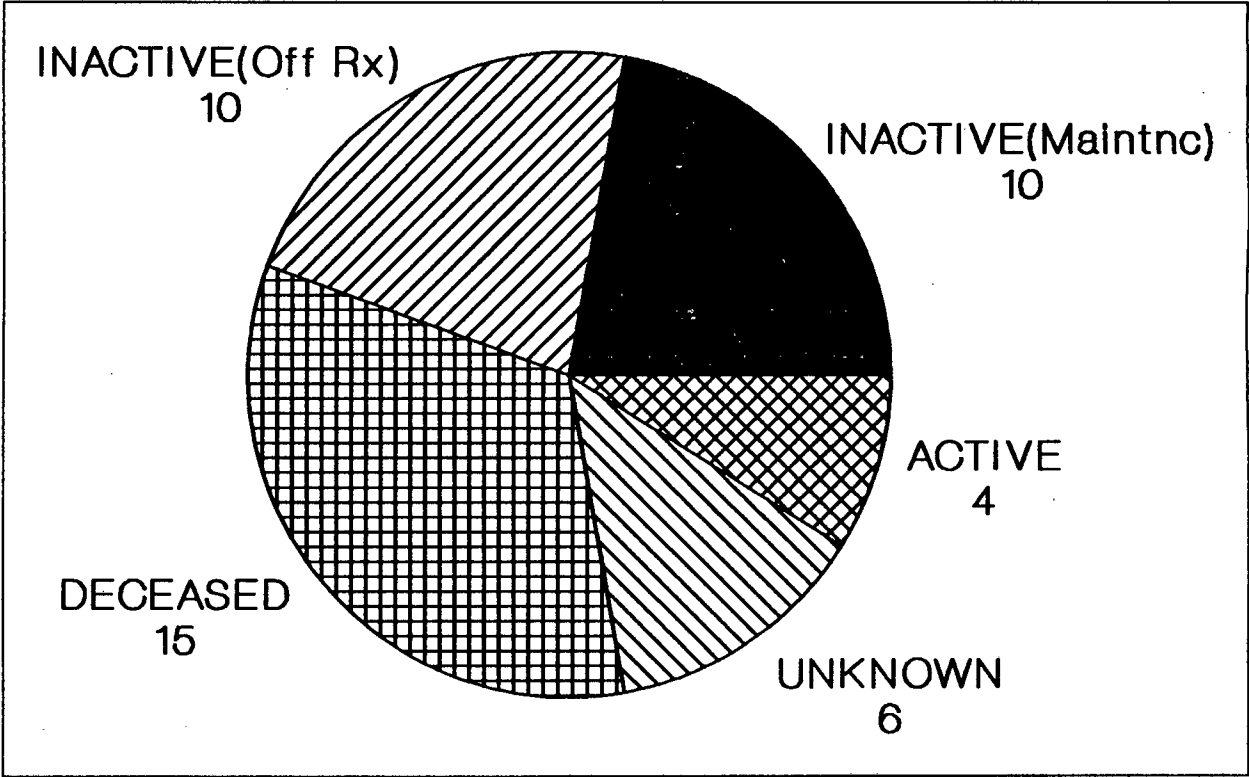
Duration of first episode of PG varied from six weeks (case 31) to 18 years (case 33). In 22 patients the course lasted between 1 and 5 years, in 16, it was less than 1 year and in the remaining 7 patients it was longer than 5 years.

Recurrences were documented in 5 patients (i.e. a recurrence being regarded as development of PG at least 1 year after the previous episode and where patient had been off all therapy for PG, for the same period.) Intervals between recurrences varied from 16 months (cases 4, 22) to 12 years (case 15). The remaining two patients (cases 33 and 36) had periods of inactivity of approximately 2 years. Thirty-seven patients (from the clinical history available) could be regarded as the acute, rapidly progressive form of PG, while the remaining 8 patients followed a more slowly progressive pattern.

PRESENT STATUS (November 1990) (Figure 13)

Ten patients had inactive disease off therapy, 10 were in remission on maintenance, 4 had active disease (3 on corticosteroid treatment, 1 on homeopathic medication), 13 are deceased and the status at time of writing was unknown in 6.

Figure 13 : Status of patients in GSH series (November, 1990)



DECEASED

- | | |
|------------------|---|
| Cases 18-22, 25 | from underlying associated disease |
| Cases 26,32, 39 | following complications as a direct result of cutaneous disease |
| Cases 44, 45 | following complications of therapy for cutaneous disease |
| Case 37 | due to unrelated causes |
| Cases 23, 38, 43 | unknown causes |

ASSOCIATED DISEASES

Thirty-one patients had an associated disease (tables 3a & 3b). Of these, 13 had IBD, 6 had a haematological disorder, 4 were associated with rheumatoid arthritis, 3 had CAH and 1 each suffered from Takaysu’s arteritis, Behcet’s syndrome, endometriosis, systemic vasculitis and an IgA gammopathy (figure 14). The associated disease preceded development of PG in 21 patients, coincided in 8 and occurred after a considerable period in the remaining 2.

TABLE 3a : THE ASSOCIATION OF PG WITH SYSTEMIC DISEASES

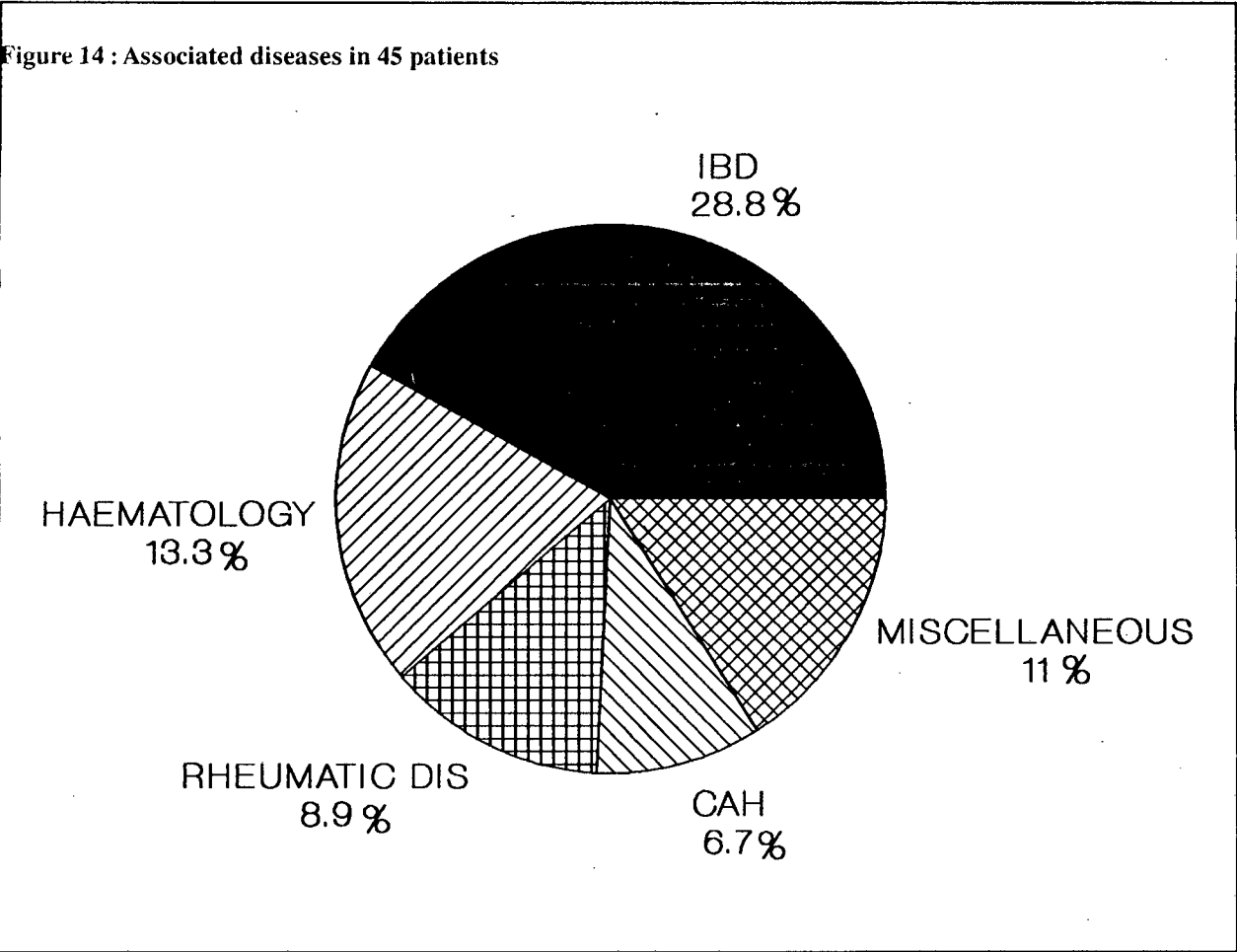
No Pat	Sex	Age and year of onset of PG	Associated disease	Age and year of onset associated disease
1 GS	F	36 years (1975)	Crohn’s	43 years (1982)
2 LJ	F	26 years (1986)	Crohn’s,	15 years (1981)
3 MI	F	26 years (1985)	Crohn’s	21 years (1980)
4 MI	F	41 years (1987)	CUC	41 years (1987)
5 NS	F	57 years (1989)	CUC	21 years (1989)
6 LN	F	40 years (1989)	Crohn’s, Ankylosing spondylitis	35 years (1984) 36 years (1985)
7 RH	F	55 years (1982)	Crohn’s	51 years (1980)
8 CC	F	30 years (1988)	Crohn’s,	22 years (1980)
9 AN	M	37 years (1980)	CAH CUC	33 years (1976) 21 years (1965)
10 AG	M	20 years (1975)	Crohn’s	10 years (1965)
11 PC	F	43 years (1978)	Crohn’s	37 years (1972)
12 RN	F	19 years (1980)	Crohn’s	17 years (1978)
13 EW	F	31 years (1985)	Crohn’s	31 years (1985)
14 GS	F	51 years (1981)	RA +ve	42 years (1972)

TABLE 3b : THE ASSOCIATION OF PG WITH SYSTEMIC DISEASES

No Pat	Sex	Age and year of onset of PG	Associated disease	Age and year of onset associated disease
15 SS	F	47 years (1975)	RA -ve	38 years (1966)
16 SA	F	41 years (1977)	RA -ve	21 years (1959)
17 PM	F	63 years (1984)	RA +ve	55 years (1976)
18 PH	M	59 years (1981)	AML	59 years (1981)
19 WJ	M	67 years (1987)	Myelodysplasia	64 years (1984)
20 MS	F	72 years (1987)	Myelofibrosis	59 years (1974)
21 PS	M	67 years (1985)	Myelodysplasia	66 years (1984)
22 ??	F	19 years (1984)	AML	19 years (1984)
23 MB	M	71 years (1971)	AML	71 years (1971)
24 AV	F	18 years (1989)	CAH	13 years (1984)
25 AB	M	24 years (1973)	CAH	20 years (1969)
26 FB	F	11 years (1985)	CAH	8 years (1982)
27 AL	F	18 years (1984)	Takayasu's arteritis	18 years (1984)
28 SP	F	45 years (1976)	Endometriosis	43 years (1974)
29 NB	M	20 years (1975)	Behcet's syndrome	20 years (1975)
30 MM	F	17 years (1988)	Systemic vasculitis	17 years (1988)
31 NM	M	64 years (1990)	IgA gammopathy	64 years (1990)

Abbreviations: CUC = Chronic ulcerative colitis
RA +ve = Seropositive rheumatoid arthritis
RA -ve = Seronegative rheumatoid arthritis
AML = Acute myeloid leukaemia
CAH = Chronic active hepatitis

Figure 14 : Associated diseases in 45 patients



INFLAMMATORY BOWEL DISEASE (IBD)

IBD was the most common associated disease and was seen in 13 patients (28.8%) (cases 1-13). Of these, 10 (76.9%) had Crohn’s disease and 3 (23.1%) ulcerative colitis. Eight patients had active inflammatory bowel disease at the time their skin lesions developed. One asymptomatic patient demonstrated ulcerative colitis on radiographic examination. She had no bowel symptoms at the time she developed pyoderma gangrenosum and none had developed at follow-up 2 years later (case 4). One patient noted an exacerbation of her exist-

ing pyoderma gangrenosum with a flare of the bowel activity (case 6). Three patients had inactive bowel disease at the time of development of their skin lesions (cases 1, 2, 3).

HAEMATOLOGICAL DISORDERS

Six patients had an associated haematological disorder (cases 18-23). Three had acute myeloid leukaemia (cases 17, 22, 23), 2 had myelodysplasia (cases 19, 21) and 1 (case 20) had myelofibrosis. All had active haematological disease at the time of diagnosis of PG. In one, the PG resolved when the underlying haematological malignancy was treated with cytotoxics. This same patient had a recurrence of pyoderma gangrenosum which coincided with an exacerbation of the acute myeloid leukaemia, during which flare she died. (This case was a subject of a previously published report²⁹). One patient's pyoderma gangrenosum healed completely following pulse medrol therapy and never recurred despite deterioration of her myelofibrosis, from which she ultimately died (case 20, figure 8). One patient (case 21) died with a large recalcitrant lesion of his right thigh still present (figure 15) which failed to respond to several modalities of treatment. His myelodysplasia, although stable, never completely remitted, and he eventually died from his underlying disease. The PG lesion remained virtually unchanged for a period of 2 years.

Another patient who presented with pyoderma gangrenosum and was found to be suffering from acute myeloid leukaemia, died of overwhelming organ failure within 5 days of the diagnosis being made, despite the institution of cytotoxic therapy (case 18). The fifth patient developed PG approximately 3 years after a diagnosis of myelodysplasia was made, and the skin lesions resolved completely after oral prednisone therapy (case 19). He died of complications of the haematological disease 4 months after the skin lesions had healed.

Figure 15 : PG associated with myelodysplasia (case 21)



All six patients in this group are deceased. Three are known to have died with lesions of pyoderma gangrenosum present, two had none and the follow-up of the sixth patient is unknown.

ARTHRITIS

Four patients (cases 14-17) had RHEUMATOID ARTHRITIS (2 seronegative, 2 seropositive). One (case 17) had active arthritis at the time she developed PG, while the remaining three were in remission on therapy. In the seronegative group, none demonstrated bowel symptomatology, although radiographic evidence of inflammatory bowel disease was not sought. One of these, (case 15) developed her PG at site of hip surgery (Figure 16).

Figure 16 : PG occurring at site of surgery



Three patients in the IBD group were documented as suffering from arthritis (cases 2, 6 and 8). Cases 2 and 8 had arthritis of the "colitic" type and radiographic evidence of erosive arthritis was lacking. Patient 6 was found to be suffering from ankylosing spondylitis and had radiographic evidence to support this. Of the remaining patients in the GSH series, vague arthralgias were mentioned in some, but exact details were not available.

CHRONIC ACTIVE HEPATITIS (CAH)

Four patients were documented as having an associated chronic active hepatitis (cases 9, 24-26). Of these, case 9 had ulcerative colitis as well (and was included in the group with IBD). In this case, the CAH developed eleven years after a diagnosis of ulcerative colitis was made.

All 4 patients developed their cutaneous lesions between two and four years after CAH was diagnosed.

Patient 25 has since died from his associated disease. Of the remaining three, case 9 had no recurrence of PG at follow-up 9 years later and the CAH was stable on treatment; patient 24 had no active lesions at time of writing (6 months after last flare of PG) and was stable on treatment, while case 26 continued to have active skin lesions at the time of writing and attempts at stabilizing the CAH were in progress (with initial indications of success.)

OTHER DISEASES

Rare associations were present in 5 patients (cases 27-31). One each suffered from Behcet's syndrome, Takayasu's arteritis, endometriosis, systemic leucocytoclastic vasculitis, and one was found to have an incidental IgA gammopathy on serum protein and immunoelectrophoresis. In the first two patients, cutaneous lesions suggestive of PG were already present at the time the associated disease was diagnosed, but were only recognized as PG much later. Endometriosis was diagnosed in case 28 prior to the development of PG and case 30 developed renal vasculitis several weeks after PG was diagnosed, while the patient with the IgA gammopathy (case 31) presented with a readily recognizable lesion of PG and no appar-

ent underlying associated disorder, until immunoelectrophoresis revealed the IgA paraprotein.

IDIOPATHIC PG (Table 4)

In 14 patients with PG, no evidence of an underlying systemic disorder was found. Eleven were male. No pattern with regard to age, clinical presentation, course or prognosis emerged in this group when compared to the associated disease group except for the preponderance of females (21 of 31 patients, 67.7 percent) in the latter as opposed to the relatively few females (3 of 14, 21.4 percent) in the idiopathic group.

TABLE 4: IDIOPATHIC PYODERMA GANGRENOSUM

NO.	PATIENT	SEX	AGE AT ONSET OF PG
32	WL	M	63 years (1971)
33	PO	M	16 years (1963) *1
34	DF	M	8 years (1985)
35	RJ	F	28 years (1989)
36	PE	M	11 years (1958) *2
37	CB	M	65 years (1976)
38	MN	F	34 years (1977)
39	AM	M	10 years (1978)
40	MB	M	34 years (1988)
41	MA	F	14 years (1972)
42	NS	M	46 years (1974)
43	JT	M	64 years (1969) *3
44	TP	M	42 years (1981)
45	GT	M	34 years (1978)

**1,2,3: These patients were included in this series as diagnosis of PG was made after 1970, although skin lesions were present for much longer (see case reports).*

LABORATORY INVESTIGATIONS

The following investigations were done routinely in all patients at time of diagnosis (irrespective if an associated disease was known to be present or not): Full blood count, erythrocyte sedimentation rate (ESR), serum biochemistry, blood glucose, VDRL, Chest X-ray.

In the idiopathic group, all of these investigations were normal or negative, except in 5 patients with extensive cutaneous disease, where the ESR was significantly raised (based on values for the GSH laboratories) (cases 38, 39, 43, 44, 45). These 5 patients also had evidence of a normochromic, normocytic anaemia of chronic disorders. Two of these patients (cases 44, 45) had evidence of old pulmonary tuberculosis on chest X-ray at the time they developed PG (both subsequently developed active pulmonary tuberculosis while on corticosteroid therapy for their skin lesions).

In the associated disease group, abnormalities in the routine investigations were usually appropriate for the associated disease. The VDRL was negative in all patients in this group.

Results of serum protein electrophoresis were available in 29 patients (12 were in the idiopathic group).

No paraproteinaemias were present in the associated disease group (polyclonal, non-specific elevations were present in 7).

In the idiopathic group, only one patient (case 31) was found to have a benign IgA gammopathy (urine was negative for Bence-Jones protein). In one other patient (case 34), with normal serum protein and immunoelectrophoresis, light chains of 40 and 20 kappa were detected in the urine, but their significance was not determined (this patient completely re-

covered after a short course of corticosteroid and dapsone therapy). Serum protein electrophoresis in the remaining 10 patients was either normal or showed a non-specific polyclonal elevation. Immunoelectrophoresis was not routinely requested in the GSH series.

TESTS OF DELAYED HYPERSENSITIVITY

(Mantoux or Candida intradermal test)

Tests of delayed hypersensitivity were recorded in 12 patients. Strongly positive mantoux reactions were present in 4 patients, 3 of whom were found to have active pulmonary tuberculosis (patients 26, 44, 45). The fourth patient had an associated endometriosis but no evidence of active tuberculosis (case 28). Five patients were non-reactive to intradermal tuberculin, while the remainder were recorded as "normal".

BOWEL STUDIES

ASSOCIATED DISEASE GROUP (31 patients)

Barium studies were undertaken in 7 patients in this group:

Four of these patients had IBD and bowel studies were done at the time of development of PG:

Case 1 - revealed long-standing Crohn's disease (this was diagnosed 8 years after onset of severe oral ulceration).

Case 2 - a retrograde barium study through the ileostomy showed no evidence of recurrent Crohn's disease.

Case 4 - barium enema was done as part of the work-up for patients with "idiopathic" PG and revealed the radiological evidence of ulcerative colitis (the patient was clinically asymptomatic).

Case 5 - PG and bowel symptomatology occurred at almost the same time. Barium enema and rectal biopsy confirmed the presence of ulcerative colitis.

The remaining 3 patients, cases 28-30, who had associated endometriosis, Behcet's syndrome and systemic vasculitis, respectively, all had normal gastro-intestinal tracts on screening.

IDIOPATHIC GROUP (14 patients)

Screening for IBD was undertaken in 13 patients of this group. Only 1 (case 4 - who has now been included in the associated disease group) showed evidence of IBD, while the remaining 12 had normal gastro-intestinal studies.

TESTS OF IMMUNE FUNCTION

Immune function i.e. neutrophil killing time, chemotaxis, phagocytosis were undertaken in 2 patients who had extensive, severe cutaneous disease (cases 39, 45). Neutrophil killing time was 0% (100% in control), but with normal chemotaxis and phagocytosis in case 45. Neutrophil function in case 39 was normal.

Tests for connective tissue disorders (polyarteritis nodosa, systemic lupus erythematosus, mixed connective tissue disease) were undertaken in patient 30, but these were all negative or normal at the time of writing.

HISTOLOGY

Reports of histologic examination of the PG ulcers were available in 30 patients, with 53 specimens available for examination (although one was able to judge from dates on pathology reports when in the disease course specimens were taken, the site, stage of development or whether subsequent biopsies were taken from the same lesion or "new" lesions, was unavailable.)

Predominance of neutrophils in the upper dermis was demonstrated in 24 specimens.

A mixed, chronic inflammatory dermal infiltrate (plasma cells, neutrophils, mononuclear cells and giant cells were present in 15 specimens).

A necrotizing/leucocytoclastic vasculitis involving the small vessels of the upper dermis was demonstrated in 8.

One specimen (from case 40, who clinically fitted the superficial granulomatous form of PG) demonstrated the described granulomatous histology, i.e. the granulomas were formed in 3 layers: the innermost layer consisted of neutrophils, the surrounding layer was composed of giant cells and histiocytes; and the outermost layer consisted of plasma cells with eosinophils.

Twelve specimens had panniculus present, 6 demonstrating mild involvement of the subcutaneous fat, while in the remainder, the panniculus was uninvolved.

THERAPY

Details of therapy are shown in Tables 5 and 6

TABLE 5 : THERAPY

	NO. OF PATIENTS	REMISSION ON Rx	REMISSION OFF Rx	PERSISTENT PG ON Rx
STEROID				
ALONE	10	2	6	2
STEROID +				
OTHER AGENTS	28	14	7	7
OTHER AGENTS	6	-	3	3
UNKNOWN	1	-	-	-
SKIN GRAFTS	4	2	1	1

Thirty-one of 45 patients (84.4%) obtained remission of their skin ulceration on systemic corticosteroids. Five of these remitted after pulse therapy (cases 5, 17, 20, 31, 40) while the remainder responded to oral prednisone in dosages that varied between 40 and 80mg daily, except for 1, (case 27) who required up to 150mg/daily.

Three patients (6.6%) are known to have obtained complete remission without systemic corticosteroids:

Case 16 - healed after a protracted course of topical corticosteroid ointment.

Case 22 - remitted after a course of cytotoxic treatment.

Case 36 - responded to dapsone therapy.

Details of therapy were lacking in one patient (case 23).

Time for complete remission of ulceration after initiation of corticosteroid therapy varied between 3 weeks and 3 years. In the corticosteroid responsive group, 30 obtained remission under 16 weeks, while the remaining 3 ran more chronic, protracted courses (cases 1, 3, 27).

Ten (22.2%) patients failed to remit. Seven of these, despite administration of systemic corticosteroids (cases 2, 21, 26, 33, 39, 44, 45), while the remainder:

Case 12 - Refused corticosteroid therapy. Continued with active disease on homeopathic medication.

Case 18 - succumbed to underlying disease before definitive treatment could be instituted.

Case 42 - had active lesions of PG which had partially responded to oral tetracycline treatment, at his last recorded visit (figure 17).

Four patients (cases 5,10,33,34) with resistant or extensive skin lesions had skin grafts under corticosteroid cover. The grafts were successful after the first attempt in cases 5 and 34.

Case 10 eventually remitted after several procedures. However, case 34 had persistent localised PG despite repeated skin grafts.

Figure 17 : PG on oral tetracycline (case 42)



TABLE 6 : TREATMENT

PATIENT	PREDNISONE (max. daily dose)	OTHER AGENTS (daily dose)	COMPLICATIONS	STATUS IN NOVEMBER 1990
1. G.S.	60mg	Sulfasalazine 4G 6MP 75mg	Osteoporosis Hypertension Cushingoid Myopathy	Alive. Off Rx. No PG for 2 years. Bowel inactive for 18 months.
2. L.J.	125mg	6MP 75mg Sulfasalazine 3G	Cushingoid	Alive with persistent peri- neal ulceration. IBD stable on Rx. Off steroid Rx.
3. M.I.	60mg	Sulfasalazine 4G	Cushingoid Osteoporosis	Alive. No PG for 3 years. IBD stable on Rx.
4. M.I.	60mg	Sulfasalazine 4G Dapsone 100mg	Nil	Alive. No PG for 1 year. Off Rx
5. N.S.	1G	Clofazamine 300mg Sulfasalazine 4G	Diabetes mellitus. Hypertension Osteoporosis Cushingoid	Alive. No PG for 11 months on no Rx. IBD stable on Rx.

PATIENT	PREDNISONE (max. daily dose)	OTHER AGENTS (daily dose)	COMPLICATIONS	STATUS IN NOVEMBER 1990
6. L.N.	60mg		Cushingoid Hypertension	Alive. No PG for 6 months on corticosteroid. IBD stable on Rx.
7. R.H.	40mg		Nil	Alive. No PG for 7 years. IBD stable. Off Rx.
8. C.C.	60mg		Nil	Alive. No PG for 2 years. IBD stable. Off Rx.
9. A.N.	40mg		Nil	Alive. No PG for 9 years. IBD/CAH - stable on Rx.
10. A.G.	80mg		Cushingoid Myopathy	Alive. No PG for 12 years. IBD stable. Off Rx.
11. P.C.	60mg		Unknown	Unknown. Last record 12/1/79; alive. Active PG on Prednisone.
12. R.N.		Homeopathic	None	Persistent PG. Active IBD.
13. E.W.	40mg		Nil	Alive and well. No PG. Off Rx.

PATIENT	PREDNISONE (max. daily dose)	OTHER AGENTS (daily dose)	COMPLICATIONS	STATUS IN NOVEMBER 1990
14. G.S.	40mg	Dapsone 100mg Clofazamine 300mg.	Nil recorded	Unknown. Last record 9/1/84. No PG for 5 months. Off Rx. RA stable on NSAID.
15. S.S.	60mg	Sulfasalazine 4G.(added on second relapse)	Mania Cushingoid Osteoporosis	Alive. No PG for 1 year. Off Rx. RA stable- off Rx.
16. S.A.	--	Topical corticosteroid	Nil	Alive. No PG for 7.5 years. RA stable on Rx.
17. P.M.	1G	Cyclophos- phamide 1G.	Mania Diabetes mellitus.	Unknown. Last record 25/9/87. No PG. On maintenance Prednisone.
18. P.H.		Cytosine VP16 Adriamycin		Deceased (19/2/81) due to underlying leukaemia. Persistent PG.
19. W.J.	40mg		Nil recorded	Deceased (myelo- dysplasia) At time of death no PG for 3 months. Off Rx.

PATIENT	PREDNISONE (max. daily dose)	OTHER AGENTS (daily dose)	COMPLICATIONS	STATUS IN NOVEMBER 1990
20. M.S.	1G		Nil	Deceased (3/89) (myelofibrosis) At time of death no PG for 2 years. On Rx for under- lying disease.
21. P.S.	40mg	Clofazamine 300mg. Methotrexate 5mg weekly Sulfasalazine 1G.	Osteoporosis Fracture right neck of femur	Deceased 27/7/88 from underlying myelodysplasia. Persistent PG at time of death. On Rx.
22.		Cytosine Arabinoside doxorubicin	Nil	Deceased from underlying leukaemia. Active PG at time of death.
23. M.B.		Unknown.	Unknown	Unknown. Last record 26/1/1972. Active PG. Rx not recorded.
24. A.V.	60mg	Azathioprine 100mg Colchicine 1mg	Cushingoid	Alive. No PG for 3 months. CAH stable on Rx.

PATIENT	PREDNISONE (max. daily dose)	OTHER AGENTS (daily dose)	COMPLICATIONS	STATUS IN NOVEMBER 1990
25. A.B	20mg		Nil recorded	Deceased (due to complications of CAH). Status of PG unknown.
26. F.B.	40mg	Azathioprine 100mg Colchicine 1mg	Cushingoid	Alive. Persistent ulceration on Rx. CAH unstable - on Rx.
27. A.L.	150mg	Clofazamine (300mg) Doxycycline (100mg) Etretinate (75mg) Sulfasalazine (4G) Colchicine (1,5mg) Cyclosporin (100mg) Anti-TB drugs Dapsone(100mg)	Cushingoid Bronze pigment- ation.	Alive. No PG for 1 year. On maintenance corticosteroid. Takayasu's stable.
28. S.P.	80mg	Clofazamine 300mg.	Cushingoid	Deceased. Post-op septicaemia. At time of death, no PG.

PATIENT	PREDNISONE (max. daily dose)	OTHER AGENTS (daily dose)	COMPLICATIONS	STATUS IN NOVEMBER 1990
29. N.B.	60mg	Clofazamine 300mg. Dapsone 200mg	Hyperpigment- ation.	Unknown. Last record 27/7/87: No PG on Rx. Behcets in remission.
30. M.M.	60mg	Dapsone 100mg Minocycline 200mg Cyclophospha- mide 1G.	Cushingoid Osteoporosis on maintenance Rx.	Alive. Stable PG and vasculitis.
31. N.M.	1G	Sulfasalazine 4G Minocycline 200mg	Headache and vertigo	Alive. PG healed for 1 week on maintenance prednisone.
32. W.L.	40mg	Sulfasalazine 4G.	Nil	Deceased. (30/10/1971) Total organ fail- ure (cause not established). Active PG at time of death despite Rx.

PATIENT	PREDNISONE (max. daily dose)	OTHER AGENTS (daily dose)	COMPLICATIONS	STATUS IN NOVEMBER 1990
33. P.O.	80mg	Tetracycline 1G. Erythro- mycin 500mg Clofazamine 300mg Azathioprine 100mg.	Cushingoid Osteoporosis Fractures of metatarsals, achilles tendon	Alive. Active lesions of PG. On maintenance prednisone 20mg/ daily
34. D.F.	40mg	Dapsone 40mg	Cushingoid	Alive and well. No PG for 3,5 years. Off Rx.
35. R.J.	40mg	Minocycline 200mg	Cushingoid	Alive with active lesions of PG. On Rx with prednisone and minocycline.
36. P.E.		Dapsone 200mg	Nil recorded	Unknown. Last record January 87 - Alive and well. No PG for 6 years.
37. C.B.	60mg	Clofazamine 300mg	Nil	Unknown. Last recorded visit 10/3/80. Alive and well. No PG for 1 year. Off Rx.

PATIENT	PREDNISONE (max. daily dose)	OTHER AGENTS (daily dose)	COMPLICATIONS	STATUS IN NOVEMBER 1990
38. M.N.	60mg	Clofazamine 300mg Dapsone 100mg	Cushingoid	Deceased. Last record 24/10/78 - one small PG ulcer on Rx.
39. A.M.	40mg	Clofazamine 300mg Sulphapyridine 1G Dapsone 150mg Imuran 40mg	Cushingoid	Deceased (27/12/78) Extensive lesions of PG present at time of death
40. M.B.	1G	Minocycline 200mg Sulfasalazine 4G	Headache	Alive. PG healed for 1 week. On prednisone 60mg/daily.
41. M.A.	30mg	Sulfasalazine 4G	Cushingoid	Alive and well. No PG for 13 years. Off Rx.
42. N.S.		Tetracycline 1G	Nil	Unknown. Last record 17/2/75. Active PG on tetracycline.

PATIENT	PREDNISONE (max. daily dose)	OTHER AGENTS (daily dose)	COMPLICATIONS	STATUS IN NOVEMBER 1990
43. J.T.	80mg		Diabetes mellitus	Unknown. Last record 21/5/71. No PG on predni- sone 10mg/daily.
44. T.P.	160mg	Clofazamine 300mg Sulfasalazine 4G Azathioprine 100mg Thalidomide 200mg	Diabetes mellitus Cushingoid Osteoporosis	Death on. (3/12/89) due to diabetic coma Active lesions of PG present.
45. G.T.	60mg	Clofazamine 300mg	Cushingoid	Deceased (26/10/1980) Active lesions of PG at time of death.

CHAPTER FIVE

DISCUSSION

A retrospective study of this nature is prone to errors and omissions. In this case, it is made even more difficult by the fact that pyoderma gangrenosum is largely a clinical diagnosis where objective laboratory criteria are lacking. Despite this, adequate information was available in 42 of 45 patients collected in this series. The number of patients i.e. 45 diagnosed over a twenty year period, is likely to be an adequate representation of the true prevalence of this disorder at GSH, based on the experiences of workers in the field^{2,3,4,5,56,78,126}

On average, 1-3 new cases of PG were recorded annually in the GSH series. This number, despite an increased awareness of the condition in recent years, has remained constant. The relatively high number of patients in two series (both from the Mayo clinic), probably reflect a higher rate of referral to this major medical centre^{3,4}.

CLINICAL FEATURES

In the GSH study, the age and sex incidence conformed with other reported studies, with PG occurring mainly in adults of all ages. This study also reflected the relative rarity of PG in children and the very elderly as previously reported. There were no distinguishing features in the various age groups in either the published series or in the GSH series. This is reflected in the childhood cases seen at GSH, which varied from the localised, atypical PG of head and neck (figure 7, case 34) that remitted completely after a short course of oral corticosteroids, to extensive, fulminating disease as in case 39, who ultimately succumbed to his cutaneous disease despite multiple therapies, including corticosteroids. The third child in this series (case 26) had an associated CAH and was stable on therapy at time of writing. Of the two patients over 70 years (cases 20, 23), both had limited disease and both had under-

lying haematological disorders. PG remitted in case 20 after pulsed methylprednisolone, but the outcome in case 23 is unknown.

The pattern of the clinical course in PG was not emphasized in published series i.e. whether patients followed an acute, rapidly progressive course or a more chronic, indolent one. This is probably due to the fact that the clinical pattern offers very little in the way of predictive value with regard to response to therapy or ultimate prognosis. This was borne out in the GSH study, where 37 patients ran an acute, relapsing, rapidly progressive course while the remaining 8 were chronic and slowly progressive, yet response to therapy and ultimate outcome was extremely variable in both groups. Extensive cutaneous involvement is one factor which may be a poor prognostic indicator (a feature not emphasized in previously published series). In the GSH study, six patients (cases 27, 32, 38, 39, 44, 45) had greater than 50% cutaneous involvement, and all of them ran problematic courses. Of interest, all were of the idiopathic group except for case 27 who had associated Takayasu's arteritis. Five, are deceased (either as a direct result of their cutaneous involvement or due to complications of treatment), while the remaining patient with Takayasu's arteritis, after a fulminating course, was in remission on therapy at the time this study was undertaken. The poor prognosis in this group is worth noting.

ORAL PYODERMA GANGRENOSUM

PG of the oral cavity is uncommon, judging from the dearth of published case reports^{36,37,38}. In these individual case reports, the diagnosis of oral PG was aided by the concomitant presence of typical cutaneous lesions of PG. In the published series to date^{1,2,3,56,78,126}, oral PG is not mentioned as a feature in any of the reported patients. This

may indicate the rarity of oral involvement or a failure to recognise that oral involvement (if it was present) was that of PG.

In the GSH series, 4 patients (8.9%) were documented as having oral involvement (cases 1, 9, 26, 39). The oral ulceration in cases 1 and 26 have been retrospectively diagnosed as oral PG (following review of their records for this study). The ulcerative process in case 1 had resulted in complete destruction of the uvula, and highlighted the importance of considering oral PG in cases of severe oral ulceration where histologic proof of vasculitis or malignancy is lacking and bacterial, fungal and viral cultures are negative. This may lead to earlier and consistent therapy and avoid the kind of destruction that was seen in this patient. Repeated biopsies (as happened in case 1, who for many years was considered to be suffering from "limited Wegener's granulomatosis"), may also be avoided.

Case 26 presented with hoarseness several years after cutaneous PG was diagnosed. The hoarseness was associated with a flare of the cutaneous lesions as well as the underlying CAH. Repeated otolaryngologic examinations and biopsies revealed oropharyngeal ulceration and non-specific inflammatory changes of the vocal cords. She failed to respond to several courses of antibiotics and local care and only after adequate, consistent therapy with corticosteroid and immunosuppressives for the concomitant flare of CAH, did the oral ulcers and hoarseness resolve. (The possibility that the oral and laryngeal ulcers were due to PG was considered only after this study was undertaken). There has been only one published report of laryngeal involvement by PG³⁶. That subject, (who had an associated IBD and cutaneous PG), had intranasal as well as oral and laryngeal involvement. She responded favourably to a course of pulse methyl prednisolone.

In the GSH study, the oral involvement (which resolved after oral prednisone) in case 9, best fitted the description for pyostomatitis vegetans (this patient had associated CUC). In case 39, however, details of the oral ulcers were lacking from the patient's records although post-mortem examination revealed evidence of severe oral involvement.

One other patient in the GSH series, case 35, had intranasal as well as lung involvement and has been tentatively diagnosed as nasal and pulmonary PG after preliminary examinations undertaken by the otolaryngology and respiratory departments appear to have excluded Wegener's granulomatosis and infections. In addition, this patient was pregnant when PG recurred for the first time. There was no deterioration in PG as a result of the pregnant state, nor did the therapy with prednisone interfere with foetal development. PG in pregnancy has not previously been discussed in the literature. A firm diagnosis of nasal and pulmonary PG could only be made after completing further examinations and biopsies. Her cutaneous lesions have remained in remission for 12 weeks (at time of writing) on 8mg/daily methylprednisolone. If Wegener's granulomatosis and all infections are positively excluded in this patient, intranasal and pulmonary PG has to be strongly considered, in which case she may benefit from pulse methylprednisolone (as did the patient in the only published report of intranasal involvement)³⁶, or a higher dose of corticosteroid. In a report of pulmonary involvement with PG the patient responded favourably to oral prednisone 1mg/kg/day after 16 weeks¹²⁷. There are two other reports of pulmonary involvement with PG, where the nature of the pulmonary condition remained undiagnosed^{128,129}, but where clinical and radiologic abnormalities returned to normal with steroid therapy. Physicians should be aware of the existence of sterile neutrophilic lung collections to avoid unnecessary delay in diagnosis and institution of therapy.

Three patients (cases 2, 10, 28) had severe perineal involvement. These patients emphasised the care that should be taken when surgery is embarked on in this area. Preparation with hyperbaric oxygen prior to surgery has been recommended¹⁰⁴. Psychological and emotional support in such cases cannot be overstressed⁴⁹. Case 2, a young female, who has an as-

sociated Crohn's disease and a permanent ileostomy, had persistent perineal disease (figure 12) and cavitating ulcers at the time of writing while, in case 28, (who had associated endometriosis), complete obliteration of the vaginal vault was unavoidable. Case 10, a male, with a permanent stoma for chronic ulcerative colitis had severe perineal ulcers, which fortunately healed well after several plastic surgical procedures and prolonged oral corticosteroid therapy. PG in the perineal area, like oral PG, may not be readily recognised, particularly in the face of IBD.

ATYPICAL PG

Scant attention is paid to the atypical forms of PG in the majority of published series but this may reflect the rarity of these forms. In the GSH study, six patients (13.3%) fulfilled the criteria for atypical forms of PG. They included the well documented but uncommon superficial, bullous variant of PG described with leukaemic and pre-leukaemic states in two patients (4.4%) (one associated with myelofibrosis, while the other was regarded as idiopathic - patients 20 and 32 respectively). The true prevalence of this atypical form is unknown. (Even the largest of the more recently published series of PG makes no mention of this variant having occurred in any of their 86 patients)⁴.

The atypical PG of head and neck also appears to be uncommon. Six patients (24%) had involvement of the head and neck in a series of 25 patients reported by Snyder²⁴. Prystowsky et al reported that 1 of 21 patients (4.8%) had atypical PG of head and neck⁷⁸. Attention is not drawn to this variant in other published series. In the GSH study, 3 patients (6.7%) were regarded as suffering from atypical PG of head and neck (cases 5, 33, 34). Case 5, who had acute, rapidly progressive PG of the neck associated with IBD, resolved on pulse and oral corticosteroids; case 33 failed to remit despite pulse and chronic oral corticosteroid

therapy spanning a period of nearly 18 years, while case 34, a young boy with indolent lesions, responded favourably after oral corticosteroid therapy was instituted.

Finally, the one other variant of PG described in the literature, and reported by Wilson-Jones and Winkelmann i.e. the localized vegetative form of PG⁴⁶ occurred in one patient in the GSH series (case 40). Since this report, there have been no further published reports of this variant. The GSH patient illustrated both the clinical (figure 5) and histological pattern of this variant. In the Wilson-Jones report⁴⁶, it is stated that this form appears to have a better prognosis with the majority of patients resolving without systemic corticosteroid and, therefore, distinction from the other clinical variants may be indicated. However, in the GSH study, case 40 required pulse methylprednisolone for control, once again emphasising the variability in all forms of PG.

ASSOCIATED DISEASE

PG is frequently associated with a systemic disease (more than 50% in most published series). In the GSH study, 69% had an associated systemic disease.

In the GSH series, as in the majority of published reports, INFLAMMATORY BOWEL DISEASE was the most frequent association (cases 1-13). However, unlike in the other published series and reports^{5,54,74,75,77,130,131}, Crohn's disease (regional ileitis), rather than chronic ulcerative colitis, was more frequently encountered. This may reflect the high referral rate of Crohn's disease to this centre, where a special interest in regional enteritis exists. The patients in this group varied widely with regard to clinical presentation, absence or presence of bowel activity at time of development of PG, response to therapy and clinical course. This is in keeping with experience elsewhere^{54,74,75,77,130,131}.

The contentious issue of bowel resection for cutaneous disease¹⁰² was highlighted by case 2, who had persistent perineal disease at time of writing, despite radical surgery (a total colectomy, followed later by a proctectomy). This issue was addressed by Talansky et al¹⁰², who on a retrospective study of 9 patients with active PG at time of operation for inflammatory bowel disease showed two patterns of post-operative healing: (1) Prompt healing within 2 months, occurred in five patients with moderate to severe inflammatory bowel disease. (2) Skin disease persisted in four others, healing only after a year. Three of these patients had mild ulcerative colitis, and in them, the operation was carried out in the hope of curing crippling pyoderma gangrenosum. Another group of authors, Levitt et al¹³¹, have reported that in 13 patients with PG who underwent surgical resections (total of 15 procedures), PG healed promptly in five cases, only with additional therapy in five, and very slowly or not at all in five. They concluded that healing appeared to be unrelated to the timing and extent of intestinal resection. This opinion is supported by other published reports^{34,75,103}. The general consensus would thus appear to be that intestinal resection may not necessarily heal the PG of IBD and that bowel activity rather than cutaneous disease, should be considered when surgery is contemplated. This contrasts with the earlier literature which generally supported the notion that definitive surgery of bowel disease favourably influenced the skin lesions¹³².

Another problem highlighted by case 2 is distinguishing perineal Crohn's disease from perineal PG⁵². In the former, surgery may be embarked on to exclude occult abscesses or sinuses, but if the lesion happens to be PG, this may further exacerbate the existing condition. Under these circumstances, examination under anaesthesia by an experienced surgeon is paramount to avoid the risk of unnecessary surgical trauma. Except for Maule's letter⁵², the problem of distinguishing perineal Crohn's disease from perineal PG has received scant attention from gastroenterologists and ano-rectal surgeons, judging from the dearth of pub-

lished reports on this issue. Given the debilitating course (physical and emotional) of PG in the perineal area, its distinction from perineal Crohn's disease warrants further attention. Patients with perineal PG may benefit from pulse methylprednisolone therapy.

Parastomal PG occurred in five patients in the GSH study. This relatively high number of patients may indicate an increasing awareness of this entity by gastroenterologists, dermatologists and stomatherapy nursing staff at this hospital since attention was first drawn to it by McGarity et al in 1984⁴⁷. Since this report, there has been one further report⁴⁸. Parastomal PG may be difficult to recognise since parastomal dermatitis, ulceration and abscesses are common. The diagnosis, as for PG elsewhere, should be one of exclusion (particularly infection). The ulcers of PG in this area may not show the typical appearance of PG elsewhere on the skin, but a compelling feature for PG observed in the GSH series, was the intense pain at the site, followed by a dramatic reduction in intensity (sometimes within hours) after the introduction of corticosteroids. This prompt reduction in pain is not discussed in McGarity's report where oral prednisone was prescribed in 3 patients with parastomal PG⁴⁷. The one other report of parastomal PG that is available, described the successful use of a wound gel rather than systemic therapy in a patient with parastomal PG⁴⁸.

The overall prognosis in the IBD group in the GSH series was good. (10 of the 13 patients were alive and well at time of writing, with no active disease, either on maintenance or off treatment altogether; one (case 13) had persistent disease on homeopathic medication; follow-up in one (case 11) was unavailable but at the last recorded visit the ulcer was showing signs of healing, and case 2 had persistent perineal disease). It would appear that PG in association with IBD may run a less severe course.

ARTHRITIS is an often quoted association with PG, but some confusion exists as to the true prevalence of sero-positive rheumatoid arthritis associated with PG as opposed to other forms of arthritis i.e. sero-negative rheumatoid arthritis, arthritis of inflammatory bowel disease, ankylosing spondylitis and osteoarthritis. In only 2 series, was close attention paid to the forms of arthritis occurring with PG^{4,56}. In the latter series, Holt et al, drew attention to a unique form of erosive, destructive polyarthritis associated with PG. Unfortunately, in the GSH study, accurate documentation of the presence of arthritis was available in six patients only. Despite this, it would appear that none of the patients in the GSH series suffered from the seronegative erosive, destructive form of polyarthritis described by Holt et al and thought to be peculiar to patients with PG⁵⁶. A more careful examination of joints in future patients with PG may yield more accurate figures.

Cutaneous vasculitis in rheumatoid arthritis may be of grave prognostic significance¹³³. PG in rheumatoid arthritis has in the past been distinguished from rheumatoid vasculitic ulcers on morphological grounds and the absence of vasculitis on histology, yet this distinction may not be valid in the light of vasculitis having been demonstrated in lesions diagnosed as PG⁸⁰. An overlap of cutaneous vasculitis and PG may exist, as illustrated in a patient in the GSH series (case 17) who had digital infarcts, small haemorrhagic infarcts of face, mononeuritis multiplex and large cutaneous ulcers diagnosed as PG by the dermatologists. A more careful look at the clinical presentation and histologic picture in patients with PG and rheumatoid arthritis may help to clarify this issue.

An unusually high association of HAEMATOLOGICAL DISORDERS with PG (13%) was found in the GSH study (6 of 45 patients). This may reflect the high index of suspicion displayed by the haematologists at this hospital, who in 1985 reported a patient with PG in association with acute myeloid leukaemia²⁹. The prevalence of PG in association with

leukaemic and pre-leukaemic conditions in other series is low (1 of 86 patients in the Mayo clinic series, 1 of 10 patients in the Waikato experience)^{4,126}. As previously reported, patients with myeloid malignancies who develop pyoderma gangrenosum have a particularly poor prognosis^{25,30}. This is reflected in the GSH series, where all six patients have died from their underlying disease. In 3 patients (cases 18, 22, 23), the course was rapidly downhill, while the remaining 3 (cases 19, 20, 21), who ran more indolent courses, were plagued by ill-health and debility throughout their illness. Four patients died with persistent cutaneous disease (cases 18, 21, 22, 23), while in the remaining 2 (cases 19, 20), the PG lesions had remitted on oral and pulse corticosteroid therapy, respectively.

CHRONIC ACTIVE HEPATITIS (CAH) is an uncommon but well documented association with PG^{6,7}. Two of the 86 patients (2.3%) with PG in the Mayo clinic series suffered from CAH⁴. There were none in the other published series^{1,2,3,5,56,78,126}. The GSH study revealed an unusually high number of patients with CAH (4 of our 45 patients, 8.9%). One of these patients had CUC as well (Case 9). Some confusion with the hepato-cutaneous syndrome¹³⁴, a chronic skin eruption of trunk and limbs associated with CAH and characterised by inflammatory papules with central crusting, which on healing, leave depressed scars, and PG, arose in case 25 at her initial presentation. However, as the lesions evolved into more typical lesions of PG which lacked the specific histology described for the hepato-cutaneous syndrome (i.e. a dermal infiltrate of lymphocytes and histiocytes with patchy quantities of fibrin in the sub-basal region of the skin), a confident clinical diagnosis of PG was made in this patient.

The relatively high number of cases of PG is association with CAH in the GSH series, again may reflect an increased awareness of this association on the part of hepatologists and dermatologists at this institution.

MONOCLONAL GAMMOPATHIES (particularly IgA) have been reported in association with PG with increasing frequency in recent years^{56,71,78,87}. The incidence of monoclonal gammopathy with PG varies in different series.

Ten percent of patients with PG (9 of 86) were found to have a monoclonal gammopathy in the series reported from the Mayo clinic⁴. Holt et al and Prystowsky et al reported IgA gammopathies occurring in twenty percent of their patients i.e. 3 of 15 and 4 of 21 patients respectively^{56,78}. None of the 15 patients studied by Lazarus and Hickman had a monoclonal gammopathy⁵. Kyle and Greipp have also reported that ten to twenty percent of patients with PG have a monoclonal gammopathy¹³⁵.

In the GSH study, only one patient had an IgA gammopathy on immunoelectrophoresis (case 31). This may be due to the fact that immunoelectrophoresis has as yet, not been part of the routine investigations in PG at this institution. Thus far, reports indicate that the majority of monoclonal gammopathies associated with PG tend to run a benign course^{71,78}.

The importance of the association remains unclear, but with reports of some patients developing myeloma later on in their course⁷¹, long-term observation of these supposedly benign monoclonal gammopathies is probably indicated. Holt and Prystowsky recommend that serum protein electrophoresis be done in every patient with PG^{71,78}. Kyle and Greipp have pointed out that a small monoclonal peak may be missed on serum protein electrophoresis and therefore perhaps immunoelectrophoresis should be done in all cases of PG¹³⁵. In the GSH series, immunoelectrophoresis was not done in those patients where serum protein electrophoresis was normal or a polyclonal acute phase response was obtained. With increased awareness of the association of monoclonal gammopathies with PG, the recognition of such patients at GSH may well increase, particularly if immunoelectrophoresis is routinely requested on all cases of PG.

The significance of less commonly associated diseases remains speculative. In the GSH study, there was 1 patient each with Behcet's syndrome (case 29), Takayasu's arteritis (case 27), systemic leucocytoclastic vasculitis (case 30, figure 18) and endometriosis (case 28).

Figure 18 : PG associated with systemic vasculitis (case 30)



This reflects the uncommon occurrence of these rarer disorders with PG and confirms the experience of series previously reported in the literature. The patient with endometriosis (case 28) in the GSH series, is thought to be the first patient in whom endometriosis has been described in association with PG⁵⁰. The role of endometriosis in the pathogenesis of

PG in this patient remains speculative. The patient with Behcet's syndrome ran a chronic indolent course that required relatively low doses of oral prednisone (10mg/daily maintenance) to control, yet when he stopped taking his medication, he would almost immediately experience a flare of the cutaneous disease. Skin lesions, typical of PG, have been reported in Behcet's syndrome.^{66,136,137} Munro and Cox report an extensive clinical and histological overlap between pyoderma gangrenosum and Behcet's syndrome⁶⁶.

Figure 19 : Extensive cutaneous disease in a patient with Takayasu's arteritis (case 27)



Case 27, who had Takayasu's arteritis, had extensive, fulminating disease (figures 19 and 20) and yet, after prolonged corticosteroid therapy attained complete remission. (At the time of writing she had been in remission for one year and was stable on a maintenance dose of prednisone 10mg/daily). PG in association with Takayasu's arteritis has been reported with greater frequency from Japan, where the increased incidence remains unexplained. No correlation between site of arterial obstruction and site of PG was detected in the 96 Japanese cases thus far reported, although it has been suggested that peripheral circulatory insufficiency may play a role⁹⁰.

Figure 20 : Extensive cutaneous disease in a patient with Takayasu's arteritis (case 27)



Case 30 demonstrated both cutaneous and renal vasculitis. This patient presented with symptoms of a systemic illness (mass loss, fever, arthralgia, anaemia), then subsequently developed haemorrhagic looking vesiculo-pustules, some of which evolved into ulcers that were diagnosed by dermatologists as that of PG (figure 18) (histology of a vesico-pustule demonstrated leucocytoclastic vasculitis). Leucocytoclastic vasculitis has been previously reported in the literature^{57,59}. In the first, leucocytoclastic vasculitic skin lesions preceded the development of PG by 8 years, while in the second the vasculitic lesions preceded PG by 3 years. In both patients, evidence of systemic involvement was lacking. In the second report, the patient had an associated chronic pyelonephritis. The patient in the GSH study appeared to be suffering from a vasculitic syndrome which had not yet clearly been defined (the attending physicians expect this patient to evolve into SLE with time). Renal vasculitis in association with PG has not previously been reported but an association with systemic lupus erythematosus (SLE) has⁹².

Of note, 3 patients in the GSH study developed pulmonary tuberculosis sometime during the course of their illness, but this may not be a significant association with PG in the face of the high incidence of pulmonary tuberculosis seen in the Western Cape.

Of these 3 patients, the first presented with pulmonary tuberculosis at the same time he developed PG (case 45), the second had evidence of old healed pulmonary tuberculosis at presentation of PG (case 44), while the third patient developed signs and symptoms of TB while on corticosteroid therapy prescribed for PG and the associated CAH (case 26).

Lazarus and Hickman reported 1 patient with pulmonary tuberculosis in association with PG⁵.

HISTOPATHOLOGY

Su et al, who examined the largest number of specimens taken from lesions of PG, concluded that a lymphocytic vasculitis was frequently demonstrated when the biopsy was taken from the advancing, peripheral zone of erythema, while a mixed inflammatory infiltrate and abscess formation was found in those cases where specimens were taken from the undermined edge or floor of the ulcer⁵⁵. In Su's study, it is not clear whether the early vesiculo-pustular lesions of PG were biopsied. Callen found that these early pustular lesions always demonstrated a marked neutrophilic infiltrate in the dermis which justified the classification of PG under the neutrophilic dermatoses⁵.

In the GSH study, 53 specimens from 30 patients were available for study, none of which showed a lymphocytic vasculitis. This may indicate that none of the biopsies were taken from the peripheral zone of erythema present adjacent to the undermined edge, as advised by Su et al⁵⁵. Wong and Greaves support the view that leucocytoclastic vasculitis is a pathogenetic factor in PG⁵⁷. Neutrophils were the predominant cells in 24 specimens (45.3%) (including those where a leucocytoclastic vasculitis was demonstrated). In Su's study, 36 specimens (55%) demonstrated neutrophils. It is now accepted that leucocytoclastic vasculitis is often present if the very early vesiculo-pustular lesion of PG is biopsied⁵⁷. Leucocytoclasia was demonstrated in 3 of the 66 specimens studied by Su et al i.e. 5 percent⁵⁵. It is not clear whether fibrinoid necrosis was present as well in these specimens. It is interesting that in the GSH study, as many as 8 of the 30 patients biopsied (26.6%) demonstrated leucocytoclastic vasculitis. In these 8 patients (cases 3, 4, 30, 31, 34, 37, 41, 43) biopsies were taken from clinically characteristic lesions of PG in 7, while the remaining patient (case 34), presented with the atypical variant of PG of the head and neck. In patient 30, leucocytoclastic vasculitis was demonstrated in both skin and kidney.

It would thus seem that histologic evidence suggests that the initiating event in PG may be a vasculitis, but until such time as a large enough series is undertaken, this supposition remains speculative.

IMMUNOPATHOLOGIC STUDY

Documentation of direct immunofluorescence having been done on specimens taken from lesional or peri-lesional skin of patients with PG, was lacking in the GSH study.

Direct immunofluorescence was done in two studies^{78,138}. In the first, Prystowsky et al did not detect any deposition of complement or immunoglobulin in biopsies of the leading edge of ulcers of PG, while Powell et al described positive immunoglobulin or complement present in lesional skin of 61 percent of 51 cases studied by immunofluorescence. This seems to indicate that at this stage, this examination is not particularly helpful in elucidating the pathogenesis of PG.

SPECIAL INVESTIGATIONS

Hypersensitivity skin testing.

Judging from the literature review, delayed hypersensitivity tests as a routine investigation are of questionable value in PG⁷⁸. In the Western Cape, however, the mantoux intradermal test is probably indicated in all patients with PG in view of the high incidence of tuberculosis in this region, as the majority of patients with PG will require corticosteroids.

Radiology

The value of chest radiography is not discussed in the literature, although the recent reports of lung involvement in PG^{127,128,129} highlight the value of this investigation. In the Western Cape, where the prevalence of pulmonary tuberculosis is high, chest radiography is of particular importance, especially in patients embarking on corticosteroid therapy. Preliminary investigations in case 35 suggest that her pulmonary lesions may be sterile neutrophilic collections associated with PG.

The value of barium studies of the upper and lower gastro-intestinal tract (possibly combined with sigmoidoscopy or colonoscopy) in the patient without symptoms of bowel disease is controversial. Perry, in one of the earlier series, felt that, in view of the frequent association of chronic ulcerative colitis with PG, all patients with PG should have a complete gastro-intestinal radiological screen³. Patients who did not have a proctoscopic examination or a colon roentgenogram were placed in the category of inadequate gastro-intestinal study³. In Perry's study, 44 of 62 patients (71%) had adequate gastro-intestinal studies and of these 31 were found to be suffering from chronic ulcerative colitis (of these 25 had colitis prior to onset of PG). Only four (9.1%) asymptomatic patients were found to have radio-

logical evidence of bowel disease. In the GSH study, adequate bowel studies were undertaken in 15 patients who had no symptoms relevant to the bowel. Of these, 1 was found to have radiographic evidence of CUC (case 4). Eighteen months later, when she had a recurrence of PG, bowel screening showed no evidence of CUC. On follow-up two years later, she remained asymptomatic. The remaining 14 patients had completely normal gastrointestinal tracts on screening. Two patients with bowel symptoms at, or soon after the development of PG (cases 1,5), were found to have IBD on barium studies. One other patient, known to have Crohn's disease of longstanding, was asymptomatic for bowel disease (radiologically and clinically normal) at the time she developed PG (case 2).

Callen, too, recommends routine studies of the gastro-intestinal tract, but this recommendation does not appear to be based on sound data⁷. Judging from the Perry, Mayo clinic and GSH series, it seems hard to justify routine gastro-intestinal radiography in patients without signs or symptoms of bowel disease.

THERAPY

Evaluation of therapy is very difficult in a disorder that runs an unpredictable course and is subject to remissions and exacerbations. This problem is compounded in PG by the lack of uniformity in approach to treatment and the many drug regimens recommended. In the GSH series, systemic corticosteroid therapy was the favoured treatment, either alone or in combination with other agents in 38 patients (84.4%). Favourable responses occurred in all (complete remission was obtained in 27, partial healing in the remainder). In the GSH series, the starting dose of oral prednisone (or maintenance dose after pulse therapy), was 1mg/kg/day, in all cases. Pulse therapy (1G methyl prednisolone intravenously daily for 3 days) was administered in 5 patients (11.1%) in the GSH series. In 4, it was administered specifically for the cutaneous disease (cases 20, 31, 33, 40) while in the remaining patient,

the major indication was for the associated disease, rheumatoid vasculitis (case 17) with favourable response being obtained for both the systemic and cutaneous disorders. Where the pulse was given for the cutaneous disease alone, 3 obtained remission (cases 20, 31, 40) while the fourth (case 33) had only partial healing at the time of writing. Pulse therapy was first recommended for PG in 1982¹¹¹ (3 patients were treated). The same group of authors subsequently treated 8 patients (6 successfully) with this form of treatment⁷⁸. A much larger group of patients should be studied before the efficacy of pulse therapy in PG can be evaluated.

Steroid-induced complications were recorded in 18 patients in this study and included osteoporosis, diabetes mellitus, hypertension, moon facies, striae, and truncal obesity (refer to table 4 for individual patients). Four patients developed serious infections while on corticosteroid therapy (pulmonary tuberculosis in 3 - cases 26, 44, 45 - and systemic nocardiosis in the fourth (case 27). One patient sustained a fracture of the neck of femur (case 21) and another (case 33) suffered bilateral fractures of his achilles tendons while on oral prednisone for PG.

Side-effects of adjuvants used in the GSH series included bronze pigmentation due to clofazamine (in two patients, cases 27 and 29), renal impairment due to cyclosporin, neutropaenia due to cyclophosphamide and azathioprine in case 27 and intolerable headache on sulfasalazine in two (cases 31 and 40).

In the earliest of the published series, Brunsting employed general measures in the form of blood transfusions, adequate diet, tanning via a quartz mercury-vapour lamp, local measures aimed at reducing inflammation and oral medication in the form of potassium

iodide and arsenic, all of which met with varied responses¹. The impression was that the disease course was in no way influenced one way or the other by the measures employed.

In the GSH study, one patient (case 16) healed after a protracted course of topical steroid ointment and local measures (presumably, systemic therapy was not considered as the ulcers were relatively small and limited to the legs).

In a 1957 study, Brunsting and Perry reported "good" responses in 9 of 13 patients (69.2%) treated with salicylazo-sulfapyridine (sulfasalazine). This included 3 patients without CUC. However, details of extent of cutaneous disease, length of treatment and exact dosage for maintenance, time taken to healing etc. are lacking from this report². Subsequently, sulfapyridine and sulfone-type drugs were found to be effective in PG¹⁰⁸.

In the GSH study, sulfasalazine was used as an adjuvant with corticosteroids in 12 patients and sulfapyridine in 1. Neither of these drugs were chosen as first line of treatment in any of the patients. In the GSH series, diaminodiphenylsulfone (dapsone) was chosen as first-line in one patient (case 36) with good effect. Despite this, it was not the drug of choice in subsequent cases of PG seen at GSH. Since the reports of Perry (1957) and Lorinez (1962), the sulphonamides appear to have been relegated to role of adjuvants after corticosteroids were shown to be unquestionably effective in PG. In the GSH series, the addition of sulfasalazine and sulfapyridine appeared not to have any influence on the overall pattern of PG in the patients where it was prescribed.

Adrenal steroids have been administered systemically for over 32 years¹¹⁰. Perry in his report of 62 patients with PG in 1969, stated that the trend of therapy at that time was toward the use of sulfapyridine, either alone or in combination with corticosteroids. He found systemic corticosteroids particularly valuable when the PG was fulminating and destructive³.

This has certainly been the trend in the GSH series, where the majority of patients responded favourably to corticosteroids.

Clofazamine has been reported as being effective in PG¹¹³⁻¹¹⁵ and was the drug of choice in 1 patient (case 29) in the GSH series, but response was poor (healing occurred only after corticosteroid was added.) Clofazamine was continued together with oral prednisone in this patient but appeared not to influence the overall course of PG. Other agents that were tried in combination with corticosteroids in the GSH series included minocycline, azathioprine, cyclosporin and thalidomide, all of which appeared to have dubious effects on the overall course of PG. Many factors such as inadequate dosage, length of trial period, lack of careful documentation may have led to this negative impression of adjuvants and their efficacy will thus have to be established with a more controlled study of corticosteroids with and without adjuvants, over a long period, to resolve this issue. Agents other than corticosteroids (given the serious side effects of these agents even at relatively low-dosage levels) are always being sought. Cytotoxics may be indicated for severe and extensive disease^{119-122,139}. Intravenous cyclophosphamide and methylprednisolone, as recommended for rheumatoid vasculitis by Scott and Bacon¹⁴⁰, may be a wise choice in the light of increasing evidence that PG may be a vasculitic process and given the debilitating nature and poor prognosis of extensive PG.

CHAPTER SIX

SUMMARY

Forty-five patients were diagnosed as suffering from pyoderma gangrenosum (PG) at Groote Schuur hospital over a twenty-year period.

The majority of patients appeared to follow the acute, rapidly progressive pattern of the disease, while a small number apparently followed the more indolent, slowly progressive course described for some cases of PG.

The age, sex, morphology of the skin lesions, presence or absence of an associated disease and presence or absence of vasculitis in tissue taken from the cutaneous lesions, appeared to have no influence on response to therapy or overall prognosis of this condition. The extent of cutaneous involvement, however, did appear to adversely affect the course of the disease when large areas were involved.

Corticosteroid therapy was the mainstay in the majority of patients and although it appeared to result in a favourable response in many, its influence was largely unpredictable. The role of adjuvants was dubious but lack of detailed case notes may have led to this negative conclusion.

The successful use of the Scott and Bacon protocol ¹⁴⁰ in 2 patients in the GSH series (cases 17,30) for underlying rheumatoid vasculitis and systemic leucocytoclastic vasculitis, respectively, was noted to result in the resolution of their PG lesions as well.

This study highlighted some of the problem areas in PG, namely, establishment of clinical patterns, relationship of associated disease (when present) to the cutaneous disorder; role

of adjuvants and pulse therapy in management; role of vasculitis in pathogenesis of PG and the unpredictability of responses to therapy. Another aspect highlighted was the importance of detailed case notes in poorly understood disorders like PG. This would allow for valid conclusions to be drawn on various aspects of the disease in a retrospective study of this nature.

The results of this study have led to recommendations (that include a format for the diagnostic evaluation, follow-up and therapeutic suggestions in patients with suspected PG) which hopefully, will lead to improved management of these patients in the future.

The GSH experience has confirmed that PG is an uncommon condition, but nevertheless a crippling, distressing disorder for the individual patient while for the attending physician it remains a diagnostic and therapeutic dilemma.

CHAPTER SEVEN

RECOMMENDATIONS

PATIENT MANAGEMENT

Based on the literature review and this study of GSH patients, the following approach to the patient with PG is recommended :

FIRST VISIT (DIAGNOSTIC EVALUATION)

NAME, DATE OF BIRTH, SEX.

HISTORY

- Age at onset
- Clinical appearance at onset
- Time for development of established ulcer
- Precipitating trauma
- Presence of pain (mild, moderate, severe)
- Joint pain
- Associated disease

EXAMINATION

Number, size, site of active lesions. Extent of scars of previous ulcers. (Diagram).

Routine physical examination (to include signs of associated disease activity if present; detail of arthritis if present).

Sideroom : Haemoglobin; urine for protein, blood, glucose; stool for occult blood.

ASSESSMENT

- (1) Probable PG

(2) Classic PG

*PLAN**LABORATORY INVESTIGATIONS*

- Chest X-ray
- Full blood count
- Serum biochemistry (including renal, liver function tests and blood glucose level)
- Skin biopsy (from peripheral zone of erythema and/or early vesicopustule if present) for histology and cultures (bacterial, fungal, viral)
- Serum protein electrophoresis and immunoelectrophoresis.
- Radiological studies of gastro-intestinal tract (only if indicated from history and/or physical examination).
- Appropriate serological tests to assess degree of activity of associated disease if present.

*THERAPY**PROBABLE PG*

Local care and analgesia until PG confirmed.

CLASSIC PG (see flow chart)

MANAGEMENT OF ASSOCIATED DISEASE (if present)

PROGRESS CHART

(Two weekly visits for first six weeks, four weekly thereafter).

HISTORY

- Pain in lesions
- Size of lesions
- New lesions
- Activity of associated disease (if present).

EXAMINATION

Size, site, number of active lesions (diagram).

Healing NO/INCOMPLETE/COMPLETE

Extension YES/NO

Side effects of corticosteroids/other medication

Activity of associated disease (if present)

Results of laboratory investigations (highlight abnormalities)

ASSESSMENT:

PLAN

THERAPY (see flow chart)

MANAGEMENT OF ASSOCIATED DISEASE (if present)

THERAPY FLOW CHART

**Rapidly Progressive
(limited)**

Slowly Progressive

**Severe, extensive
PG**

**Prednisone
1mg/kg/day
X 2/52**

Good Response

**Continue at this
dose until
healed then
taper to
maintenance**

Poor Response

**Hospitalise
for pulse
therapy**

Good Response

**Continue on
maintenance
prednisone**

Poor Response

**Repeat pulse
weekly X 2**

Good Response

maintenance prednisone

Poor Response

**Consider Scott/Bacon
Protocol ¹⁴⁰**

**Hospitalise for IV
cyclophosphamide and
methylprednisolone
(Scott & Bacon) ¹⁴⁰**

SUGGESTED RESEARCH PROJECTS

(that might be done in Cape Town)

- (a) **CLEAR DOCUMENTATION OF CLINICAL PATTERNS OF PG** prior to and after commencing therapy (may offer better prognostic evaluation than in the past). This should include size, number, site, extent of cutaneous involvement, pattern of presentation and progression, response to standardized therapy, (including time to healing), activity of associated disease and its influence (if any) on the cutaneous disease.
- (b) **PATTERNS OF POLYARTHRITIS IN PG** (to see whether the unique pattern of arthritis elicited by Holt et al is present in patients with PG seen in the Western Cape)⁵⁶.
- (c) To determine the **VALUE OF CYTOTOXICS** alone or as adjuvants in recalcitrant cases of PG.
- (d) To determine the incidence of **MONOCLONAL GAMMOPATHIES** in PG in Cape Town, using immunoelectrophoresis in all cases.
- (e) A careful **CLINICO-HISTOPATHOLOGICAL STUDY** (with particular care taken that biopsies are taken from early vesicopustules and/or the peripheral erythematous zone of advancing lesions) to establish the role of vasculitis in PG.

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APPENDIX

CASE REPORTS

INFLAMMATORY BOWEL DISEASE

CASE 1 : MRS G.S. (Date of birth 04/12/1939)

April 1975	Severe oro-pharyngeal ulceration. Histology : Chronic inflammatory cells. Diagnosis : "limited" Wegener's granulomatosis." (In view of severity despite lack of histologic proof). Treatment : Prednisone 40mg/daily. Healed promptly.
September 1975	Off prednisone. Oral ulcers recurred together with a vesiculo-pustular rash. Histology : no vasculitis. Diagnosis : Wegener's granulomatosis. Treatment : Oral prednisone. Skin and oral lesions healed.
Sep 1975 - Nov '81	Repeated episodes of oral ulceration and vesico-pustular rash occurred when prednisone was tapered below 20mg/daily.
November 1981	Watery diarrhoea but barium studies normal.
August 1982	Pyoderma gangrenosum of left calf. Recurrence of oral ulcers (Still regarded as limited Wegener's granulomatosis, no vasculitis, normal chest X-ray) Treatment : Prednisone. Complete resolution.
February 1983	Melaena. Barium studies - "Crohn's disease of long standing". Treatment : Maintenance prednisone increased. Course: Symptoms resolved.
January 1984	Leg PG, oral ulcers, diarrhoea recurred. (Prednisone had been stopped). At this stage, markedly cushingoid, osteoporotic, hypertensive, myopathic. Uvula completely destroyed. Treatment : Prednisone 40mg/daily. 6 Mercaptopurine (6MP) 50mg/daily.
February 1984	Skin and oral ulcers healed. Prednisone tapered to 20mg/daily.
March 1984	Slight flare of oral ulcers. 6MP increased to 100mg/daily.

May 1986	For more than two years, had required frequent increases of oral prednisone from 15mg/daily to 40mg/daily for 2 to 3 week periods at a time to control oral ulcers and bowel symptoms. (Had no further cutaneous PG since January, 1984).
June 1986	Prolonged total parenteral nutrition (12 weeks) substituted for chronic corticosteroid therapy Response : Good.
September 1986	Stable off all systemic treatment.
October 1986	Acute arthritis of left ankle. Treatment : Sulfasalazine 3G/daily. Good response.
Nov 86 - May 88	Remission. No systemic treatment
June 1988	Severe flare of oral ulceration. Bowel asymptomatic. Treatment : 6 Mercaptopurine (6MP) 75mg/daily. Ulcers resolved completely.
April 1989	Remission maintained on 6MP 75mg/daily.
May 1989	Stopped taking 6MP.
September 1990	Established that she has maintained this last remission. Has had an occasional flare of oral ulceration and bowel disease. (Both usually mild, clearing spontaneously after a day or two) No further PG.

COMMENT *This is probably a case of oral PG, in which case the oral lesions preceded the development of skin lesions by several years (unlike the reported cases where the oral lesions coincided with the development of cutaneous PG)³⁶⁻³⁸.*

CASE 2 : MISS L.J. (Date of birth 13/07/1966)

July 1981	Severe Crohn's disease diagnosed. (Terminal ileum, colon, rectum involved). Treatment : Oral prednisone 40mg/daily. Total parenteral nutrition. Predsol enemas.
August 1981	Defunctioning colostomy performed. (Due to failure of above treatment to control symptoms). Treatment : Post-operatively - 100mg hydrocortisone down ileostoma / daily.
October 1981	6 Mercaptopurine (6MP) 50mg/daily added.
June 1982	Symptoms persisted - total colectomy performed. Rectum left in situ. 6MP stopped. Treatment : Post-operatively - Prednisone 50mg/daily.
June 82 - Aug 86	Stable. Gradually weaned off oral corticosteroids altogether.

September 1986	Acute, non-erosive arthritis of left knee. (Three weeks after stopping prednisone). Treatment : Non-steroidal anti-inflammatory (diclophenac) - settled.
September 1986	One week after acute arthritis, developed peristomal "abscess" and two weeks thereafter, perineal ulceration. Treatment : Antibiotics, Predsol enemas.
January 1987	Pyoderma gangrenosum of peristomal and perineal regions diagnosed. No evidence of bowel activity on barium studies. Treatment : Prednisone 60mg/daily. 6 MP 50mg/daily.
March 1987	PG healed. Bowel asymptomatic.
May 1987	Weaned off prednisone but still on 6MP 50mg/daily.
December 1988	Remission. 6MP stopped.
March 1989	Acute arthritis left knee. Treatment : Diclophenac.
August 1989	Recurrence of perineal ulceration. Bowel inactive. (clinically and radiologically). Treatment : Prednisone 80mg/daily. Dramatic reduction in pain but healing of ulcers was slower.
October 1989	Noted that : "large anal cleft ulcer persists." Sulfasalazine 3G/daily added to regimen.
December 1989	Prednisone tapered to 20mg/daily. Perineal ulceration persisted. Bowel inactive. Proctectomy with resection of caecum and terminal ileum performed. Post-op Treatment : Prednisone 20mg/daily. Sulfasalazine 3G/daily.
January 1990	"Ongoing perineal sepsis." Patient weaned off steroids.
February 1990	Deterioration of perineal ulceration. Diagnosis : PG. Treatment : Prednisone 125mg/daily. Sulfasalazine 3G/daily.
April 1990	Active ulceration absent. Large cavity occupied the perineum. Treatment : Prednisone 50mg/daily. Sulfasalazine 3G/daily.
June 1990	Noted that perineal wound had decreased in depth but adjacent skin showed little evidence of healing. Prednisone was considered to have little effect and patient was advised to wean herself off completely.
September 1990	Peristomal "excoriation" noted. Perineal wound was thought to be smaller but margins were tender. Treatment : Sulfasalazine 3G/daily. Off prednisone.
COMMENT	<i>This patient illustrates the diagnostic and therapeutic dilemmas faced by the attending physicians of the patient with Crohn's disease who presents with perineal ulceration. Although a sarcoid-like histology may help to differentiate perineal Crohn's from perineal PG, its absence does not necessarily preclude a</i>

diagnosis of regional ileitis. Such patients, either way, may benefit from a course of pulse methylprednisolone.

CASE 3 : MISS M.I. (Date of birth 08/12/1959)

1980	Diagnosis : Crohn's disease. Treatment : Oral corticosteroids Course : Stable.
June 1985	Pyoderma gangrenosum. (Slowly progressive superficial ulcers of both lower legs). Histology : (early vesicopustule) Leucocytoclastic vasculitis of upper dermal vessels. Bowel in remission. Treatment : Prednisone 60mg/daily. Dapsone 100mg/daily. Course : Completely healed over 16 weeks.
Nov 1985 - Jan 1986	Limited recurrences occurred at any attempt to reduce prednisone below 20mg/daily.
February 1986	Sulfasalazine 4G/daily substituted for dapsone. Made no difference. Still unable to achieve control below prednisone 20mg/daily.
January 1987	6MP 100mg/daily substituted for sulfasalazine. Still unable to reduce prednisone below 20mg/daily without a flare.
July 1987	Crohn's disease flared. Treatment : Prednisone increased from 20mg/daily to 40mg/daily. 6MP continued. Course : Completely healed after 10 weeks. Bowel remitted.
November 1987	Weaned off oral prednisone with no flare of skin or bowel. 6MP stopped.
November 1987	No further episodes of PG.
November 1990	Has continued to have intermittent flares of Crohn's disease that are readily controlled on systemic therapy (usually corticosteroid).
COMMENT	<i>No clearcut relationship between bowel activity and skin ulceration could be demonstrated in this patient. Although her overall course was one of slow progression, this was while on treatment. The fact that she rapidly deteriorated with lowering of the prednisone below 20mg/daily indicates that she in fact falls into the acute, rapidly progressive group of PG.</i>

CASE 4 : MRS M.I. (Date of birth 18/01/1946)

- July 1987 Pyoderma gangrenosum of left scapular region (figure 1). Rapidly progressive. No bowel symptoms but barium studies (done as part of screening tests in PG) revealed evidence of ulcerative colitis. Treatment : Prednisone 60mg/daily. Sulfasalazine 3G/daily. (In view of bowel findings).
- August 1987 Bilateral salpingo-oophorectomy. (Under corticosteroid cover) - large ovarian mucinous cyst adenoma removed. Laparotomy site healed with no problem.
- October 1987 PG healed. Patient weaned herself off corticosteroids and stopped taking sulfasalazine.
- January 1988 PG (1 x 2cm ulcer) developed on right shin. Bowel remained asymptomatic. Treatment : Topical medium potency steroid ointment. Course : Healed over 3 weeks.
- January 1989 Recurrence of PG overlying right ankle. Bowel asymptomatic. (Repeat barium studies - normal). Treatment : Prednisone 60mg/daily. Sulfasalazine 3G/daily (Sulfasalazine prescribed despite normal bowel studies because of previous rapid response). Course : Completely healed in 3 weeks.
- September 1989 Remained healed. Off systemic treatment. Patient has emigrated. No further follow-up available.

COMMENT *Asymptomatic inflammatory bowel disease has been reported to occur in patients with PG.^{3,7} The IBD changes are detected radiologically, when barium studies are done as part of the routine work-up of "idiopathic PG". In this patient, all evidence of IBD disappeared 18 months later. She remained asymptomatic with regard to bowel symptoms throughout her course.*

CASE 5 : MRS N.S. (Date of birth 01/01/1940)

- May 1989 Pyoderma gangrenosum of head and neck (figure 4). Rapidly progressive ulcerative lesion. (atypical PG) Ulcerative colitis diagnosed at the same time. (Watery diarrhoea for 4 months prior to ulceration). Treatment : Oral prednisone 60mg/daily x 1 week, failed to halt ulcerative process. Given pulse Methylprednisolone 1G IVI/daily. Split skin graft done under corticosteroid cover. Donor site healed with no problem. Course : 100% take of skin graft. Bowel symptoms resolved.
- September 1990 Established that PG and ulcerative colitis have remained in remission on Sulfasalazine 3G/daily and clofazamine 100mg/daily. (Patient had been successfully weaned off corticosteroids several months previously).

COMMENT *This patient had rapidly progressive ulceration of right side of neck that did not have the characteristic clinical appearance of PG, but resolved on adequate doses of corticosteroids. This patient best fits the description given by Anderson²³ who coined the term "malignant pyoderma". This term is now felt to be misleading¹⁸ and the alternative, "pyoderma gangrenosum of the head and neck" is thought to be more acceptable. Rapid recognition of pyoderma gangrenosum when it occurs at atypical sites is important because of the potentially destructive nature of this disorder and because the disease may be more responsive to therapy in the early stages. In suspected cases, high-dose corticosteroid therapy should be instituted as soon as tissue has been obtained for appropriate microbiologic and histopathologic studies.*

CASE 6 : MRS L. N. (Date of birth 05/12/1949)

February 1984	Diagnosis: Crohn's disease. Treatment : Intermittent course of oral prednisone with good effect.
November 1985	Diagnosis: Ankylosing spondylitis. Treatment: Non-steroidal anti-inflammatory drugs. Course: slow progression.
July 1989	Pyoderma gangrenosum of left shin. (Following trauma). Bowel asymptomatic. Treatment : Prednisone 40mg/daily. Sulfasalazine 4G/daily. Course : Healed rapidly over six weeks. (Prednisone tapered to zero over 8 weeks).
March 1990	Crohn's disease flared. Rapid recurrence of PG at the same site. Treatment : Prednisone 60mg/daily. Course : Rapid resolution of bowel symptoms associated with complete healing of pyoderma gangrenosum in two weeks.
May 1990	Failed to take prednisone for one week. Acute and rapid deterioration of both bowel and PG (at the same rate). Again, prompt healing with re-institution of prednisone therapy.
September 1990	Remission on Prednisone (bowel and skin).

COMMENT *This patient's PG was clearly responsive to corticosteroids. She again demonstrates that occurrence of PG is not always associated with IBD activity. Sulfasalazine was not added on the second relapse of PG. It remains to be seen if remission is sustained when the prednisone is tapered to zero.*

CASE 7 : MRS R.H. (Date of birth 21/05/1927)

1962	3rd degree vaginal tear while delivering twins. Failed to heal completely.
1969	Recto-vaginal fistula.
April 1970	Defunctioning colostomy prior to repair of recto-vaginal fistula.
July 1970	Following surgery, discharging sinuses developed at colostomy scar (which had been closed subsequently) and at site of recto-vaginal fistula repair. Diagnosis : ? Crohn's disease. Barium studies : "extensive diverticulosis". Treatment : Conservative.
July 1970	Sinuses persisted and extended.
May 1974	New sinus developed spontaneously in left iliac fossa. Non-functioning kidney (chronic glomerulo-nephritis). Diagnosis : ? Crohn's disease. Barium studies repeated : again reported as "extensive diverticulosis." Treatment : Sinus tracts laid open. Left nephrectomy. Course : Stormy. Faecal peritonitis. Development of multiple fistulae at sites of drain insertions.
May 1978	After a protracted course, requiring many hospital admissions to manage the multiple anterior abdominal wall fistulae, a TOTAL COLECTOMY was performed. Histology of the colon revealed unequivocal Crohn's disease.
May 1978 - Jul 1982	Stable on conservative therapy (mainly stoma care).
August 1982	Developed pyoderma gangrenosum of parastomal region and left lower leg. Crohn's in remission at the time. Treatment : Prednisone 40mg/daily. Course : Healed completely over a period of 20 weeks on tapering doses of prednisone.
April 1983	Healed PG. Off prednisone.
March 1985	Small bowel enema - no Crohn's disease.
September 1990	Patient alive and well, on no systemic treatment.
COMMENT	<i>Patient developed pyoderma gangrenosum 4 years after total colectomy for Crohn's disease and at a time when Crohn's disease was not demonstrated in the small bowel. PG should be considered in patients with previous IBD, even if apparently cured, when skin ulceration develops¹⁰³.</i>

CASE 8 : MRS C.C. (Date of birth 02/04/1958)

October 1987	Total Crohn's colitis. Treatment : Oral prednisone. 6 Mercaptopurine. Response good.
December 1987	Right transverse colectomy performed.
April 1988	Treatment : post-operatively - prednisone 60mg/daily.
July 1988	Prednisone tapered then stopped over 8 weeks.
August 1988	Acute arthritis left knee, left hip, left shoulder. Flare of Crohn's colitis. PARASTOMAL PYODERMA GANGRENOSUM. Treatment : Prednisone 60mg/daily. 6MP 75mg/ daily. Response slow but favourable.
April 1989	Prednisone tapered more cautiously this time. PG healed. Arthritis and Crohn's remitted on prednisone 20mg/daily and 6MP 75mg/daily.
July 1989	Prednisone down to 5mg/daily. 6MP stopped. (neutropaenia)
July 1989	Stable
Mar 1990 - Apr 1990	Perianal "abscess". Active Crohn's of rectum and distal sigmoid. Treatment : Prednisone 60mg/daily.
July 1990	Left hemicolectomy and proctectomy. Treatment : (post-operatively) - nil systemic.
August 1990	Last recorded outpatient visit - well. No parastomal, perineal or skin lesions. Bowel in remission.
COMMENT	<i>Pyoderma gangrenosum developed after transverse colectomy. Resolved on oral prednisone therapy. The perianal "abscess" may well have been a flare of PG but this was not confirmed. It is interesting to note, that after further radical surgery, followed by no systemic therapy, patient appears to have gone into remission, with regard to both the Crohn's disease and perineal problem.</i>

CASE 9 : MR A.N. (Date of birth 04/03/1943)

1970	Chronic ulcerative colitis (CUC) diagnosed.
1972	Total colectomy performed (left with permanent ileostomy).
1976	Developed chronic active hepatitis (CAH)
1976-1980	CUC and CAH controlled on oral prednisone.
June 1980	Developed severe oral ulceration (described as "hanging cascade of pus" obscuring the uvula, with suppurative ulcers of tongue and palate). Associated with oral ulcers are PYODERMA GANGRENO-SUM of scrotum, left leg and left ear. Bowel and liver in remission. Treatment : Prednisone 40mg/daily.
August 1980	Oral and skin lesions healed.
September 1990	No further oral or skin lesions. Bowel has remained in remission, but chronic active hepatitis activity has required the addition of azathioprine. Currently stable on prednisone 25mg/alternate days and azathioprine 100mg/daily.

COMMENT *This patient developed oral and cutaneous lesions when the bowel and liver were assessed as being in remission. The differential diagnosis of the oral ulcers in this setting would include pyoderma gangrenosum, major aphthous ulcers and pyostomatitis vegetans. PG is favoured as the latter two nearly always accompany severe flares of the bowel disease. Also, the presence of PG on the skin elsewhere, supports the diagnosis of oral PG. However, as in case 1, all 3 oral lesions serve as markers of IBD, the treatment of which is expected to lead to resolution of the mucosal lesions as well. Distinguishing one from the other may be very difficult clinically.*

CASE 10 : MR A.G. (Date of birth 21/11/1956)

1965	Chronic ulcerative colitis diagnosed. Treatment: Prednisone. Sulfasalazine. Predsol enemas. Course : Fluctuating.
September 1974	Proctocolectomy. Treatment: (post-operative) Predsol enemas. Sulfasalazine.
August 1975	Pyoderma gangrenosum of lower legs and perineum. (Bowel in remission). Treatment : Methylprednisolone 64mg/daily

November 1975	Complete healing of leg PG. Partial healing of perineal PG. Methylprednisolone tapered.
December 1975	Acute deterioration of perineal ulceration. Recurrence of leg PG. Treatment : Methylprednisolone 64mg/daily. Split skin graft of perineal defect (failed). Continued oral methylprednisolone. Eventually, (March 1978) healing of leg and perineal PG occurred. Prednisone stopped.
April 1978	Healed perineal defect was closed with a gracilis-myocutaneous flap. Good healing immediately post-operatively. Off systemic corticosteroids at the time.
May 1978 - Apr 1979	Recurrent small areas of breakdown and ulceration which healed on conservative treatment.
April 1979 - Nov 1990	Apart from occasional bouts of perineal sepsis, has remained well. Bowel and skin have been in remission (off systemic treatment) since April 1979. Ileostomy functioning well.

CASE 11 : MRS P.C. (Date of birth 07/07/1935)

1972	Watery diarrhoea for 3 months. Diagnosis : ? Inflammatory bowel disease. Barium studies: NORMAL bowel. Treatment : Anti-diarrhoeal drugs. Course : Intermittent bouts of diarrhoea that responded to anti-diarrhoeal medication.
October 1978	Pyoderma gangrenosum of leg (single lesion). Bowel asymptomatic. Treatment : Methylprednisolone (dose unknown) x 1 week. Course : "Little improvement".
December 1978	Referred GSH re profuse watery diarrhoea. Barium studies repeated : unequivocal Crohn's disease. PG of right leg had extended. Treatment : Prednisone 60mg/daily. Course : Ulcer started to heal slowly over next 3 weeks. Bowel symptoms also resolved.
January 1979	Patient was referred back to her practitioner in another town and was lost to follow-up.
COMMENT	<i>The appearance of PG in patients with IBD may be a predictor of flaring bowel disease, as was demonstrated in this patient.</i>

CASE 12 : MISS R.N. (Date of birth 14/02/1961)

November 1976	Diagnosis: Chronic ulcerative colitis. Course : Unstable
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November 1978	Panproctocolectomy. Histology - Crohn's disease.
August 1981	Parastomal PG. Crohn's disease active. Patient refused oral corticosteroids. Course : Fluctuated with intermittent healing and breakdown around stomal area.
September 1990	Ongoing problems of parastomal ulceration, arthralgias, discharging vesico-vaginal fistula but still refuses to take oral corticosteroid or immunosuppressive therapy.
COMMENT	<i>This patient's PG has paralleled the underlying disease activity. She remains chronically unwell but prefers homeopathic medication. She will probably continue in this fashion until the disease process spontaneously "burns itself out". It is possible that early reports of the association of PG with CUC² included patients in whom the correct diagnosis was really Crohn's disease as this patient demonstrated.</i>

CASE 13 : MRS E.W. (Date of birth 14/07/1953)

April 1985	Diagnosis: Chronic ulcerative colitis. Course: Severe disease.
May 1985	Total colectomy. Histology : Crohn's disease.
December 1985	Extensive parastomal and laparotomy scar ulceration. Diagnosis : Pyoderma gangrenosum. Treatment : Oral corticosteroids. Total parenteral nutrition. Response : Poor.
March 1986	Ileostomy resited to left iliac fossa. Active IBD. Oral prednisone continued.
October 1986	Completely healed PG. Bowel in remission.
October 1990	Stable. On no systemic therapy.
COMMENT	<i>Healing of recalcitrant parastomal PG only after resiting the stoma, as occurred in this patient, is well recognized⁴¹.</i>

ARTHRITIS

CASE 14 : MRS G.S. (Date of birth 24/03/1930)

1972	Sero-positive rheumatoid arthritis (RA). Treatment : Non-steroidal anti-inflammatory drugs. (NSAID)
1979-1980	Treatment : Gold.
July 1982	Pyoderma gangrenosum of left lower leg diagnosed (following an injury). Rheumatoid arthritis in remission on Piroxicam (NSAID). Treatment : Methylprednisolone 48mg/daily. Dapsone 100mg/daily. Split skin graft (60% take).
August 1983	PG healed. Weaned off corticosteroid. Dapsone stopped.
January 1984	Well. No PG. Rheumatoid arthritis stable on indocid suppository, 1 nocte. No further follow-up available.
COMMENT	<i>Vasculitic skin ulcers in rheumatoid arthritis may be difficult to differentiate from the characteristic lesions of PG⁸⁰. Even the absence of vasculitis on skin histology does not preclude a diagnosis of rheumatoid vasculitis as this may be due to sampling error. Unfortunately documentation of a biopsy having been done is lacking from this patient's notes and the diagnosis appears to have been made on morphological grounds.</i>

CASE 15 : MRS S.S. (Date of birth 17/02/1928)

1966	Seronegative rheumatoid arthritis. Treatment : NSAID.
August 1975	Pyoderma gangrenosum of right lateral thigh at site of surgical scar (figure 16) and dorsum of right foot. Rheumatoid arthritis (RA) in remission. Treatment : Methylprednisolone 48mg/daily.
October 1975	PG healed.
November 1975	Weaned off corticosteroids.
May 1989	Returned (13 and a half years later) with recurrence of PG in the right iliac fossa area. RA in remission. Treatment : Prednisone 60mg/daily. Sulfasalazine 4G/daily. (for steroid-sparing and therapeutic effects).
October 1989	PG healed. Prednisone tapered gradually. Sulfasalazine continued. Failed to come for further follow-up.

- September 1990 Reliably established that patient is completely well off all systemic treatment.
- COMMENT *Two limited courses of PG, 14 years apart, with prompt and complete healing on oral corticosteroid therapy on both occasions. On the first occasion, pyoderma gangrenosum occurred 2 weeks after hip joint surgery at the site of a draining sinus. The second time, onset was spontaneous. On both occasions, the RA was inactive. A confident clinical diagnosis of PG was made. Skin biopsies were not done.*

CASE 16 : MRS S.A. (Date of birth 10/11/1977)

- 1959 Sero-negative rheumatoid arthritis. Treatment : Non-steroidal anti-inflammatories. Course : Slowly progressive but adequately controlled on non-steroidal anti-inflammatories alone.
- 1977 2 x 1cm ulcer of pyoderma gangrenosum developed on left lower leg. Slowly progressive x 3 months. Several more ulcers over both legs in the months following. Treatment : Fluorinated corticosteroid ointment. Course : Healed slowly over a period of 24 weeks.
- February 1980 Pyoderma gangrenosum recurred on left lower calf and dorsum of right foot. (Ulcers less than 3cm in size). Slowly progressive. Treatment : Fluorinated topical steroid. Course : Healed over a period of 9 months.
- September 1990 No further episodes of PG. Still attending arthritis clinic regularly. Stable on NSAID's.
- COMMENT *This patient developed small, slowly progressive pyoderma gangrenosum ulcers that healed with topical therapy alone. At the time her rheumatoid symptoms were controlled on non-steroidal anti-inflammatory drugs. Favourable responses in PG to topical therapy is well documented but is uncommon^{48,105}.*

CASE 17 : MRS P.M. (Date of birth 23/03/1921)

1976	55 years old. Sero-positive rheumatoid arthritis. Treatment : NSAID's
October 1984	Mononeuritis multiplex (with presumed cerebral, pulmonary and cutaneous vasculitis) Associated with typical lesions of pyoderma gangrenosum of sacrum, right calf, left 5th digit. Musculo-skeletal system : no objective arthritis. Treatment : Pulse Methylprednisolone and cyclophosphamide ¹⁴⁰ .
July 1985	Slow recovery. PG healed. Treatment : Prednisone 20mg/daily. (Course complicated by development of diabetes mellitus - controlled on oral agents).
January 1987	Last recorded visit to GSH. Stable on cyclophosphamide 50mg/daily (which had been introduced in September 1985 after PG healed). No further follow-up available. Current status unknown.
COMMENT	<i>This patient's skin lesions were described as "livedo-reticularis type over feet and legs, nail fold infarcts of left big toe, numerous vasculitic lesions of face and large ulcers of sacrum, right calf and left fifth digit." The large ulcers were diagnosed as PG by the dermatologists but unfortunately no record of these or the "vasculitic" lesions having been biopsied exists. Under these circumstances distinguishing PG from vasculitic ulcers may be very difficult. One can only assume that the lesions diagnosed as PG were clinically compelling.</i>

LEUKAEMIC AND PRE-LEUKAEMIC CONDITIONS

CASE 18 : MR P.H. (Date of birth 07/10/1921)

January 1981 Rapidly progressive pyoderma gangrenosum of anterior thighs over two week period. Routine full blood count - Acute myeloid leukaemia. (Confirmed on bone-marrow aspiration). Treatment : CHEMOTHERAPY (cytosine / VP16 / Adriamycin) + FULL ANTIBIOTIC COVER. Course : Rapidly downhill. Died 19/02/1981. (Cause of death : acute renal failure secondary to uncontrolled haemorrhage due to the leukaemic state). In the 3 weeks following diagnosis of PG and leukaemia, the PG lesions had continued to enlarge alarmingly.

COMMENT *As previously noted, rapidly progressive PG lesions in leukaemic states are usually indicative of severe disease³⁰. This patient did not have the bullous variety of PG described in association with leukaemia, instead the lesions started as deep-seated dermal nodules which rapidly broke down to form the characteristic clinical lesions of PG. Although no record exists of the lesions having been biopsied or cultured (except for a pus swab from which a scanty growth of acinetobacter was cultured), a confident clinical diagnosis of PG was made.*

CASE 19 : MR W.J. (Date of birth 03/06/1918)

September 1985 Myelodysplasia diagnosed (presented with refractory anaemia in June, 1983).

May 1986 Erosive vegetative lesion of right groin (bacterial, fungal, viral cultures negative, histology - non-specific chronic inflammation). Treatment : Antibiotics, topical antiseptics. Course : Slowly progressive, no healing. Myelodysplasia active. Treatment : Blood transfusions.

April 1987 Typical PG of left thigh. Treatment : Prednisone 40mg/daily. Course : Both thigh and right groin lesion healed promptly. (Right groin lesion now considered to be "atypical" PG). Myelodysplasia active. Treatment : Intermittent blood transfusions.

June 1987 Skin lesions completely healed. Weaned off corticosteroids.

August 1987 Cough, fever, acutely ill. Blast crisis. Rapid deterioration. No evidence of PG. Died 5 days after admission. Post-mortem : Pulmonary mucormycosis. Acute renal failure.

COMMENT *PG healed rapidly on corticosteroids at a time when his haematological disease was at a low level of activity. It did not recur when the underlying myelodysplasia transformed to a frankly leukaemic state associated with mucormycosis. This patient presented with the slowly progressive form of PG, despite having active underlying disease.*

CASE 20 : MRS M.S. (Date of birth 08/09/1915)

1974 Myeloproliferative syndrome.

1977 Treatment : Splenectomy. Hydroxyurea 1500mg/daily.

January 1987 Bullous pyoderma gangrenosum near right lateral malleolus (figure 8). Rapidly progressive. Myelofibrosis stable. Treatment : Prednisone 60mg/daily for a week. Course : Continued to enlarge. Treatment : Pulse Methylprednisolone 1G IVI/daily x 3 days then oral prednisone 60mg/daily. Course : Immediate reduction in pain. Gradually healed over 4 weeks. Prednisone tapered over next 8 weeks.

March 1987 Off prednisone. PG healed.

March 1989 Died following rapid deterioration in haematological disease.

COMMENT *Single episode of "atypical bullous PG" with favourable response to pulse therapy. Pulse therapy is indicated, as in this case, when lesion is rapidly enlarging despite an adequate oral dose of prednisone (1mg/kg/day). This patient developed PG when her haematological disease was relatively stable, and there was no PG recurrence when it deteriorated. Most authors of reports of PG associated with myelofibrosis, myelodysplasia and leukaemia are of the opinion that PG usually accompanies or predicts an acute relapse (days or weeks) of the underlying disease²⁵⁻³¹.*

CASE 21 : MR P.S. (Date of birth 08/07/1918)

1984	MYELODYSPLASTIC SYNDROME. Treatment : Intermittent blood transfusions.
January 1987	Pyoderma gangrenosum diagnosed (non-healing ulcer of right upper thigh for 2 years) (figure 15). Myelodysplasia "stable". Treatment : Prednisone 40mg/daily. Clofazamine 300mg/daily (added 4 weeks later when prednisone alone had no effect).
March 1987	Clofazamine stopped. Lesion static at 7cm x 6cm. Maintained on prednisone 15mg/daily.
April 1987	No change. Methotrexate 5mg/weekly Prednisone 15mg/daily continued.
November 1987	Methotrexate stopped. Sulfasalazine 4G/daily substituted.
February 1988	Fractured right femur.
July 1988	DIED. (Associated disease deteriorated acutely). PG remained unchanged from time of presentation. Was still on prednisone 15mg/daily and sulfasalazine 4G/daily at time of death.
COMMENT	<i>From the time that a diagnosis of PG was first made in 1987, the lesion remained completely static, neither advancing nor healing. Patient's major complaint was deepseated pain at the site. Repeated biopsies (including deep sections) failed to reveal anything but chronic inflammatory cells. Cultures for bacteria, deep fungi, tuberculosis and atypical mycobacteria were repeatedly negative. This patient may have benefited from pulse methylprednisolone therapy or perhaps higher doses of oral corticosteroids.</i>

CASE 22 :

(THIS PATIENT IS A SUBJECT OF A PREVIOUSLY PUBLISHED REPORT)²⁹

1984	Large necrotic ulcer of right leg. Fever. Hb 6. Full blood count and bone-marrow aspirate - ACUTE MYELOID LEUKAEMIA. Ulcer - PYODERMA GANGRENOSUM. Treatment : Cytosine arabinoside, doxorubicin, VP 16 - 213. Course : Complete remission (leukaemia). Skin lesions healed completely over 8 weeks.
1986	Relapsed (leukaemia). PG recurred at same site. Treatment : Further chemotherapy (unsuccessful). Course : Died from overwhelming sepsis.

COMMENT *Treatment of underlying disorder resulted in resolution of PG (the first time) but with recurrent disease, (associated with recurrence of PG) the same result was not achieved. The favourable response first time round, was probably related to the effect of the therapeutic agents on the underlying disease, rather than a direct effect on the ulcer. The severity of the leukaemia on the second occasion probably accounted for non-healing of PG, despite intensive chemotherapy.*

CASE 23 : MR M.B. (Date of birth 18/07/1898)

November 1971 Anaemia, loss of weight, ulcers of right leg x 2 months. Diagnosis : Acute myeloblastic leukaemia. Non-specific leg ulcers. Treatment : "Conservative".

January 1972 New ulcers developed on right thigh. Patient acutely ill. Diagnosis : Pyoderma gangrenosum. Treatment : Conservative for skin lesions. For leukaemia - "mild course of cytosine followed by thioguanine" suggested by haematologists (but no record of this having been given was available). Course : Unknown. No further follow-up in hospital folder. Last record as above.

COMMENTS *This patient had slowly progressive lesions of PG despite the underlying haematological disease.*

CHRONIC ACTIVE HEPATITIS (CAH)

CASE 24 : MISS A.V. (Date of birth 10/08/1971)

- 1984 13 years old. CAH diagnosed. Treatment : Prednisone 10mg/alternate days. Azathioprine 100mg/daily.
- June 1989 Pyoderma gangrenosum (started off as numerous vesicopustules of buttocks, elbows, wrists and backs of thighs, progressing to more typical lesions of pyoderma gangrenosum and healing with cribriform scars). Treatment : Prednisone increased to 20mg/daily. (Azathioprine 100mg/daily) CAH considered in remission.
- June 1990 Intermittent relapses and remissions of PG. Treatment : Prednisone increased intermittently to 40mg/daily. Deterioration of skin lesions usually related to deterioration of hepatitis, but this is not a constant feature.
- September 1990 Skin and liver disease in remission on prednisone 20mg/daily and Azathioprine 100mg/daily.

COMMENT *As previously reported⁹¹, the activity of the hepatitis does not necessarily parallel the activity of the skin lesions. This young woman's liver disease had progressed to such a degree that liver transplantation was being considered. When she first developed lesions, they were crops of small vesico-pustules and a diagnosis of first, papulonecrotic tuberculid and later hepato-cutaneous syndrome was considered. Chronic inflammatory histology, non-reactive mantoux, extension of lesions to more florid purplish lesions that healed in parts with cribriform scarring while the active edge advanced (even though it lacked undermining), suggested a diagnosis of pyoderma gangrenosum.*

CASE 25 : MR A.B. (Date of birth 10/10/1947)

- 1969 22 years old. CAH. Treatment : Prednisone.
- 1973 - 1976 Extensive superficial ulceration of arms, legs and trunk. Diagnosis : "Recurrent impetigo". Treatment : Antibiotics (repeated). Response - healed with extensive cribriform scars. Every relapse of skin ulceration associated with flare of liver disease. Treatment : Prednisone (for liver) but skin healed as well.

August 1976	Referred dermatologists. New ulcers on hands and legs. Diagnosis : Pyoderma gangrenosum. Treatment : Prednisone 40mg/daily. Response - PG healed.
December 1976	Off all treatment for two months (poor compliance). Marked liver decompensation and renal failure. DIED. No recorded PG at time of death.
COMMENT	<i>This patient had slowly progressive lesions of PG associated with CAH. The skin lesions were arrested by prednisone therapy, but recurred when treatment was stopped. Recognition of the skin lesions as PG led to more consistent therapy with prednisone. At the time of death, no mention is made of whether active skin lesions were present.</i>

CASE 26 : MISS F.B. (Date of birth 15/03/1974)

November 83	Post-streptococcal acute glomerulonephritis (AGN). Chronic active hepatitis (CAH). Chronic, recurrent impetigo (mainly legs).
February 1984	Prednisone and Azathioprine commenced for CAH. AGN resolved.
Nov '84 - Nov '86	Recurrent necrotic leg ulcers associated with deterioration in CAH. Healed with increases in prednisone dosages, only to relapse with reduction of prednisone below 20mg/daily. Also recurrent hoarseness for which no cause was found. Treatment : Prednisone 20mg/daily. Azathioprine 50mg/daily. (Patient was not compliant with treatment).
November 1986	Leg ulcers diagnosed as pyoderma gangrenosum by the dermatologists. Treatment : Prednisone 30mg/daily. (Azathioprine had been stopped).
Nov 1986 - Jan 1990	Chronic relapsing course of PG and CAH despite prednisone.
Feb 1990 - Jul 1990	Nephritis recurred. Ulcers problematic. Hoarseness persisted. CAH troublesome. Treatment : Prednisone 15mg/daily.
August 1990	Severe oral ulceration, including destructive lesions of the tongue and vocal cords. (Biopsies - Chronic inflammation). Ongoing leg ulcers, deterioration in liver and renal functions. Treatment : Prednisone 30mg/daily, Azathioprine 50mg/daily, Colchicine 1G/daily.
October 1990	Marked improvement in general condition with near complete healing of leg and oral ulcers had taken place. Voice had begun to return to normal.
COMMENT	<i>This young woman had required numerous admissions for both medical and dermatological problems since the age of 8 years. Lack of compliance earlier in her course may account for the progressive deterioration of underlying systemic disorder, as well as oral and cutaneous ulceration. The oral lesions may well have been PG. Oral PG has been rarely reported³⁶⁻³⁸. These patients re-</i>

sponded to high dose corticosteroid therapy. Kennedy et al³⁶ recommend that for laryngeal lesions, fiberoptic nasopharyngoscopy or direct microlaryngoscopy, for better inspection, be employed.

TAKAYASU'S ARTERITIS

CASE 27 : MISS A.L. (Date of birth 23/12/1966)

August 1982	Thrombophlebitis. Iron-deficiency anaemia. Thrombocytosis. Treatment : Iron supplements. Bedrest. Improved spontaneously.
March 1984	Extensive pyoderma gangrenosum (started on legs, subsequently involved trunk, upper limbs and face). Absent brachial, radial pulses. Bruits over femoral arteries. ANGIOGRAPHY - TAKAYASU'S ARTERITIS. Treatment : (for skin) Prednisone 60mg/daily.
May 1984	PG healed. Prednisone tapered.
September 1984	Acute deterioration of PG on Prednisone 5mg/daily. Stormy course. Rapidly progressive PG. Treatment : Prednisone increased to 150mg/daily plus the following adjuvants in sequence :- clofazamine, cyclophosphamide, doxycycline, INH, monocycline, colchicine, etretinate, dapsone, cyclosporin, anti-tuberculous therapy, (INH, rifampicin, ethambutol), azathioprine. On occasion, the addition of a new adjuvant would appear to halt the progression, but any attempt to reduce oral prednisone to below 60mg/daily would result in such a rapid deterioration, that the dose of prednisone would then have to be doubled to achieve control. Each adjuvant was tried for periods of 4 to 6 weeks before abandoning as ineffectual or for unacceptable side effects.
February 1987	Sulfasalazine 4G/daily tried. Positive response apparent. Prednisone tapered cautiously from 120mg/daily.
June 1987	Treatment : Prednisone 80mg/daily. Sulfasalazine 4G/daily. For the first time in two and a half years the PG lesions healed sufficiently for her to be discharged home "permanently". (During the two and a half year hospital stay, she was allowed home on weekends as often as possible, but this was always extremely difficult in view of the extensive dressings she required).
November 1987	Treatment : Prednisone 55mg/daily. Sulfasalazine 4G/daily. Extensive cribriform scarring but only 3 small active lesions of PG on one thigh.
December 1987	Moderate deterioration in PG. Treatment : Prednisone 150mg/daily. Clofazamine 300mg/daily substituted for sulfasalazine. Response : Healed slowly. Prednisone tapered.
August 1988	Four small active PG ulcers on legs. Treatment : Prednisone 55mg/daily. Clofazamine 200mg/daily. Developed clofazamine induced "bronze pigmentation".

September 1988 Course complicated by cutaneous and cerebral nocardiosis (from pulmonary source). Treatment : IVI Amikacin x 10 days. Co-trimoxazole 4 b.d. x 1 year then 1 b.d. indefinitely. Response : All lesions of nocardiosis resolved. Recovered completely. Remaining skin lesions of PG healed as well.

September 1990 Stable. Prednisone tapered to 10mg/daily. Clofazamine stopped in March 1990. On maintenance Co-trimoxazole 1 b.d.

COMMENT *Despite a protracted, stormy course, this young woman entered a phase of remission. (Despite a life-threatening complication of the prolonged corticosteroid therapy, i.e. disseminated nocardiosis). The response of her skin ulcers appeared to be dependent on the dose of corticosteroid and the value of the several different "adjuvants" must be seriously questioned. This patient illustrates the therapeutic dilemmas of the attending physician when confronted with a patient with such extensive disease:*

1. Side effects of high dose, long-term corticosteroid therapy.
2. Narcotic dependency (these patients often require frequent administration of narcotic analgesia to control the accompanying pain).

On review, this patient might have benefited from pulse methylprednisolone therapy, earlier in her course.

The Takayasu's arteritis had progressed slowly over the years, manifesting as moderate hypertension, mild impaired renal function and mild cardiomegaly. The majority of patients with Takayasu's and PG have been described in Japan⁹⁰. The clinical picture in the reported cases (twenty-six in the Japanese literature) is identical to those where PG is associated with diseases other than Takayasu's arteritis. The relatively high association of Takayasu's arteritis and PG in the Japanese population remains unexplained.

ENDOMETRIOSIS

CASE 28 : MRS S.P. (Date of birth 03/08/1931)

November 1975	Total abdominal hysterectomy and left salpingo-oophorectomy. (endometriod cyst of left ovary present).
April 1976	Vesico-vaginal fistula (edges of which showed histological evidence of endometriosis). Repair attempted, but edges of wound failed to heal.
July 1976	New lesions developed in addition to the perineal ulceration. Large painful ulcers developed on back and anterior abdominal wall which gradually healed on no specific therapy over 18 months.
February 1978	Vesico-vaginal fistula broke down for the third time. In addition, extensive lesions of pyoderma gangrenosum of abdomen, buttocks, legs and one ear developed. Treatment : Methylprednisolone 64mg/daily. Clofazamine 300mg/daily. Vaginal cavity surgically obliterated. Course : Patient achieved partial urinary continence. Pyoderma gangrenosum healed completely after 3 months in hospital. Discharged on maintenance dose of Methylprednisolone 16mg/daily and clofazamine 300mg/daily. Failed to return for follow-up and it has been established that patient died 1 year later after yet another attempt to correct her urinary incontinence. (Cause of death was given as post-operative "septic shock.") She apparently did not have recurrence of pyoderma gangrenosum following her discharge from Groote Schuur hospital.

COMMENT	<i>This patient is a subject of a case report that appeared in the South African Medical Journal⁵⁰. The vulval as well as cutaneous lesions responded to adequate doses of corticosteroids and clofazamine. The role which endometriosis played in the pathogenesis of PG and the vesico-vaginal fistula in this patient, remains speculative. Psychological support and counselling in patients with extensive perineal involvement should form an important part of management⁴⁸.</i>
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BEHCET'S SYNDROME

CASE 29 : MR N.B. (Date of birth 19/01/1955)

June 1975	Diagnosis : Behcet's syndrome (Recurrent oral and genital ulcers, sterile pustules, sacro-ileitis). Treatment : Fibrinolytic therapy. (phenformin + ethylestranol). Course : No improvement.
December 1975	Pyoderma gangrenosum developed over both lower legs. Treatment : Prednisone 40mg/daily. Clofazamine 300mg/daily. Dapsone 100mg/daily. (The latter added to the former two, when after six weeks, complete control of skin lesions had not been achieved). Course : All skin lesions (including oral and genital ulcers and pustules healed completely over the next 3 months).
April 1976	Polyarthrititis. Treatment : Non-steroidal anti-inflammatory drugs. Maintenance : Prednisone 10mg/daily. Clofazamine 200mg/daily. Dapsone 100mg/daily.
April 1976 - Feb 1981	Followed up in Transkei. Repeated episodes of pyoderma gangrenosum when stopped taking medication but with prompt healing on re-institution. Resulted in extensive cribriform scarring of arms and legs.
February 1981	Sacro-ileitis. Uveitis. Treatment : Bed rest. Prednisone 10mg/daily. Clofazamine 200mg/daily. Dapsone 100mg/daily.
Feb 1981 - June 1986	Stable. Stopped taking medication from June 1986.
July 1986	Deterioration. Attended a different hospital. Medication only reintroduced in December 1986. By then had developed extensive lesions of PG on lower legs and upper limbs. Treatment: Prednisone 10mg/daily, clofazamine 300mg/daily, dapsone 100mg/daily.
February 1987	Referred back to GSH for re-evaluation. At that stage, he had 1/2cm x 1/2cm lesion of PG on right shin. All treatment stopped at GSH. Within one week of stopping medication, he deteriorated slowly, with development of apthous oral ulcers, sterile pustules, enlarging of old and development of new PG lesions on the legs. Treatment : Prednisone 20mg/daily. Reponse : Healed completely within two weeks.
March 1987	Discharged back to Transkei on maintenance prednisone 10mg/alternate days. No further follow-up available.

COMMENT *Pyoderma gangrenosum has previously been reported in association with Behcet's syndrome⁸⁶. The two conditions share some features: pustules and folliculitis, pathergy, non-specific histological appearances, a range of agents used to treat either condition demonstrate a similar overlap. (Corticosteroids are the mainstay of treatment in both disorders). The above patient demonstrated*

a surprisingly good response to relatively low starting (20mg/daily) and maintenance (10mg/alternate days) doses of prednisone. His response on the second occasion indicates that dapsone and clofazamine probably contributed very little, if anything, to the clinical response on the first occasion.

LEUCOCYTOCLASTIC VASCULITIS

CASE 30 : MISS M.M. (Date of birth 03/10/1971)

January 1988	Fever, mass loss, polyarthralgia, Raynaud's phenomenon, necrotic ulcers of left elbow, right ankle. Investigations : Haematology - anaemia of chronic disorders. ESR 63. Chest X-ray, ECG, biochemistry, VDRL, streptococcal serology, cryoglobulins, protein electrophoresis, circulating immune complexes, c-reactive protein, echo-cardiogram, collagen screen, rheumatoid factor, ANF were all negative or normal. Histology of edge of ulcer - non-specific chronic inflammation. Diagnosis : "Probable collagen vascular disease. Treatment : Bedrest. Spontaneously improved.
July 1989	On-going joint pain. Vesico-pustules over proximal interphalangeal joints, knees, around ankles. Small vasculitic infarcts around left thumbnail. Bacterial endocarditis excluded. Histology : Prominent neutrophilic infiltrate in dermis. No vasculitis. Diagnosis : Early vesico pustules of pyoderma gangrenosum. (Barium studies negative). Treatment : Prednisone 60mg/daily. Dapsone 100mg/daily. Course : Skin lesions and arthralgias resolved over the following 3 months.
May 1990	Weaned off corticosteroids. Generally so well that Dapsone stopped as well.
June 1990	Polyarthralgia recurred. Treatment : Non-steroidal anti-inflammatory drugs. Response : Good.
July 1990	Acute, rapidly progressive lesions of more typical pyoderma gangrenosum developed (figure 21). Treatment : Minocycline 200mg/daily (based on favourable response of PG responding to this agent alone) ^{117,118} . Course : PG lesions healed favourably.
August 1990	While PG lesions were healing, she developed a shower of acraly distributed haemorrhage papules, histology of which revealed LEUCOCYTOCLASTIC VASCULITIS. For the first time she also developed microscopic haematuria. Diagnosis : Systemic leucocytoclastic vasculitis. Renal biopsy : Focal necrotising glomerulonephritis. Minocycline stopped. Treatment : Prednisone 60mg/daily. Pulse cyclophosphamide.
September 1990	All skin lesions healed but developed pneumococcal pneumonia. Treatment : Antibiotics Course : Resolution. Oral prednisone and cyclophosphamide continued.
October 1990	Renal and cutaneous lesions stable on therapy. Diagnosis: "Vasculitic syndrome - Probably systemic lupus erythematosus (SLE)" Plan: Continued maintenance prednisone and cyclophosphamide and await developments.

COMMENT

This patient presented with a systemic illness from the onset (fever, mass loss, anaemia, polyarthralgia) in addition to her skin lesions. An aggressive therapeutic approach was adopted with the development of glomerulonephritis, in order to prevent further renal deterioration. This patient clearly had a systemic vasculitic syndrome which, although not clearly defined, was expected to evolve into SLE. The occurrence of leucocytoclastic vasculitis and pyoderma gangrenosum in the same patient has been previously documented^{57,59}, but in these patients the PG developed several years after cutaneous vasculitis was demonstrated.

IgA GAMMOPATHY

CASE 31 : MR N.M. (Date of birth 29/11/1926)

August 1990	Rapidly enlarging ulcer of right buttock. Started spontaneously. Diagnosis : ? Atypical infection. Investigations : negative. Treatment : Surgical debridement. Antibiotics. Course : Continued to enlarge alarmingly.
September 1990	Referred dermatologists. Diagnosis : Pyoderma gangrenosum. Investigations : All negative except IgA gammopathy. Treatment : Pulse therapy (1G methylprednisolone IVI daily x 3) followed by prednisone 60mg/daily. Course : Completely healed in two weeks. On maintenance oral prednisone. (Starting dose 60mg/daily with cautious tapering planned).
COMMENT	Previously well patient with sudden onset of acutely progressive PG that responded promptly to pulse therapy. He is the only patient in the GSH series with a documented IgA gammopathy (urine for Bence-Jones protein was negative). The gammopathy was considered to be of undetermined significance. This patient should probably have an annual screen for myeloma.

IDIOPATHIC PYODERMA GANGRENOSUM

CASE 32 : MR W.L. (Date of birth 02/02/1908)

April 1971	Bullous Pyoderma gangrenosum. (Multiple, haemorrhagic bullae of both legs and right wrist that progressed to more typical lesions of pyoderma gangrenosum). No associated disease found. (In particular, no haematological disorder). Treatment : Methylprednisolone 32mg/daily. Course : "Almost" healed by July, 1971.
August 1971	Acute deterioration of existing pyoderma gangrenosum and development of new lesions (associated with a deep vein thrombosis, anaemia and haematoma of left kidney). Diagnosis : ? Malignancy. (None found). Treatment : Prednisone 80mg/daily. Course : Progressive deterioration.
October 1971	DIED. Cause of death : unknown. (Post-mortem refused).
COMMENT	Despite numerous investigations, (including laparotomy to exclude lymphoma, renal carcinoma) no cause could be established for this patient's eventual demise. A bone marrow investigation was suggested but no record of this having been done exists in the patient's notes. (A full blood count, coagulation studies, protein electrophoresis were normal). This man's rapidly progressive deterioration was suggestive of "a malignancy somewhere" but none was found. A bone-marrow investigation may well have given the answer, particularly in view of the bullous nature of the PG lesions.

IDIOPATHIC PG

CASE 33 : MR P.O. (Date of birth 22/03/1947)

1963	Right groin swelling following rugby injury. At laparotomy, ileoascending colectomy performed for presumed Crohn's but this was not confirmed histologically. Post-operatively required (over the next 14 months), four abdominal operations for poor wound healing, wound dehiscence and abdominal dehiscence. After the fourth operation, all wounds gradually healed.
December 1964	"Cysts" excised from above right eyebrow and right cheek. Healed with no problems, but a few months later, right cheek scar became swollen and within a few days softened and discharged pus. Rapidly increased to a 5cm ulcer with an undermined edge.
Dec 1964 - Dec 1966	Non-healing ulcer right cheek. Histology non-specific. Cultures (bacterial, fungal, viral) - negative. Treatment : Remained virtually static at 5cm size.
January 1967	Cluster of pustules developed on LEFT cheek. Rapidly progressed to approximately 5cm ulcer with undermined edges. Diagnosis : non-specific ulcer (histology and cultures unhelpful).
April 1968	Developed ulcer of right knee. Diagnosis : ? dermatitis artefacta. Treatment : Antibiotics / topical ointments. Course : Knee ulcer healed over a period of a year. Cheek ulcers persisted.
June 1970	Attended private dermatologist for persistent bilateral cheek ulcers. Diagnosis : Pyoderma gangrenosum. Treatment : Oral prednisone. Course : Rapid and complete healing of both lesions over a period of 16 weeks.
September 1972	Stable on maintenance prednisone.
October 1972	Went overseas. Stopped taking prednisone.
May 1973	Referred to GSH with extensive ulceration of both cheeks and bilateral ectropions. Treatment : Medrol 64mg/daily. Tetracycline 1G daily. Bilateral Wolfe grafts for ectropions once adequate healing had taken place. Course : Acceptable cosmetic result with ectropion repairs. Right cheek ulceration healed completely over a period of 30 weeks. Small area of persistent ulceration on left cheek.
September 1973	LEFT ECTROPION recurred.

- Oct 1973 - Oct 1974 Had a total of NINE plastic surgical procedures over this period to try to correct left recurring ectropion. Treatment : Methylprednisolone 20 - 40mg/daily. Tetracycline 500mg/daily. Course : Any attempt to reduce Medrol to below 20mg/daily resulted in breakdown. Vicious cycle established : breakdown - healing - ectropion - surgery - breakdown etc.
- Oct 1980 - Aug 1981 "Grumbling" pustulation of left cheek (figure 6). Treatment : Methylprednisolone 28mg/daily. Course : Complicated by development of severe osteoporosis, proximal myopathy, cushingoid features. He did not develop diabetes mellitus. Fractured both achilles tendons and metatarsal in right foot during this period.
- Aug 1981 - Mar 1983 Transferred to Johannesburg. Weaned himself off corticosteroids. Left cheek PG healed. Ectropion recurred.
- March 1983 - Dec 1983 further surgical procedures attempted to correct left ectropion. (Covered with corticosteroids during and after surgical procedures). Course : Initially good effect, but breakdown occurred 4 weeks after surgery. During one of these procedures, a lipoma was excised from right wrist and this resulted in a large PG ulcer developing in that area; this eventually healed on high-dose Methylprednisolone, 64mg/daily.
- Dec 1983 - Feb 1989 Treatment : Continuous Methylprednisolone (doses varied between 20 and 64 mg/daily). In addition, various adjuvants (tetracycline, minocycline, colchicine, erythromycin clofazamine and dapsone) were tried with minimal success as left cheek pustulation persisted and continued to deteriorate with reduction of Methylprednisolone below 20 mg/daily.
- February 1989 Azathioprine 100mg/daily added.
- August 1990 18 months of Azathioprine failed to reduce Methylprednisolone requirements below 20mg/daily.
- September 1990 Admitted for pulse Methylprednisolone 1G IVI/daily x 3 days. Pustulation completely resolved. A small fibrous papule just below left eyelid was shaved at patient's request (with the steroid cover, this appeared to be an appropriate time for this minor surgical procedure). Discharged on Methylprednisolone 16 mg/daily. Sulfasalazine 4G/daily.
- October 1990 Pustulation and tiny areas of erosion recurred at and around site of shaved fibroma. Treatment : Methylprednisolone 16 mg/daily. Sulfasalazine 4G/daily continued, with the hope that the process will eventually settle.
- November 1990 Sulfasalazine stopped (headache). Skin lesions unchanged. Patient "fed-up". Planned to wean himself off steroid and seek help from homeopath.
- COMMENT This case highlights the delay in diagnosis that often occurs in PG (even in the hands of dermatologists). PG can easily be mistaken for dermatitis artefacta, as in this man's case, where the PG appears to

be related to trauma. Although PG was only diagnosed in 1970, his history suggests that the poorly healing post-operative wounds of 1963 were probably ulcers of PG. It is interesting that the most active site for many years was an area on his left cheek which he constantly "picked" at. It would appear that high dose corticosteroid, in this case, failed to control the pathergic response. It remains to be seen if lesions remain limited, off corticosteroid treatment.

CASE 34 : MR D.F. (Date of birth 26/09/1978)

July 1986	Pyoderma gangrenosum of head and neck (figure 7). (Slowly progressive ulcerative process of scalp and face over 1 year). Child healthy. No associated disease found. (Barium studies not done). Histology : vasculitis. Treatment : Prednisone 40mg/daily. Dapsone 40mg/daily. Bilateral split skin grafts performed (once adequate healing had taken place). Course : Slow but favourable healing over 20 weeks.
January 1987	Discharged. PG stable on Prednisone 15mg/daily and Dapsone 40mg/daily. Course : Failed to come for follow-up. (Lived in a small farming community).
October 1990	Established that child is completely well and healthy and has had no further recurrence of PG.
COMMENT	Atypical PG of head and neck in a child. The favourable response to relatively short courses of oral corticosteroids, dapsone and skin grafting was unexpected. No recurrence despite "abrupt" cessation of therapy. Of note in this patient was the presence of a necrotising vasculitis of the vessels in the mid-dermis (no evidence was found elsewhere despite extensive screening).

CASE 35 : MRS R.J. (Date of birth 30/03/1961)

June 1989	Pyoderma gangrenosum developed at site of excised benign breast lump. Followed by development of PG lesions on left deltoid, right deltoid and right hip. No associated disease found. Healthy. (Barium studies not done). Treatment : Methylprednisolone 32mg/daily. Course : Healed over 8 weeks. Patient unhappy with weight gain. Stopped taking corticosteroid.
March 1990	Returned with acute recurrence of old lesions and development of new ones on left temple, left malar area and back. 18 weeks pregnant. Healthy. Treatment : Methylprednisolone 24mg/daily. Course :

	Healed over 12 weeks. Remained stable on tapering dose of Methylprednisolone.
August 1990	Delivered a healthy infant.
September 1990	Off corticosteroid for 8 weeks. Pyoderma gangrenosum of the left breast and left arm recurred. Also bloody nasal discharge. Treatment : Methylprednisolone 24 mg/daily.
October 1990	Skin lesions were almost healed. Bloody nasal discharge persisted. Loss of hearing, right ear. Chest X-ray : bilateral infiltrates. ? Pulmonary tuberculosis (no acid fast bacilli). ? Vasculitis.
November 1990	Referred to otolaryngologic and respiratory departments. Preliminary investigations: Negative for Wegener's granulomatosis, malignancy, atypical infections. Plan: Further nasal and open lung biopsies for diagnostic purposes. No definitive treatment. Continued on maintenance methylprednisolone 8mg/daily for PG. Skin lesions completely healed.
COMMENT	This patient with skin lesions of PG, bloody nasal discharge and pulmonary infiltrates may well turn out to be a case of PG with nasal and lung involvement (particularly in the light of the finding of chronic inflammatory cells only on histology and negative bacterial and fungal cultures on preliminary investigations).

CASE 36 : MR P.E. (Date of birth 31/05/1947)

April 1974	Diagnosis: Pyoderma gangrenosum of lower leg. (Non-healing ulcer for 12 years, following a rugby injury). No associated disease. Histology - vasculitis. Sigmoidoscopy - normal. Treatment : Dapsone 100mg/daily. Course : Completely healed over a period of 16 weeks. Stopped dapsone September 1974.
April 1976	Occurrence of PG (left calf)(spontaneous breakdown). Treatment : Dapsone 100mg/daily. Course : Completely healed over a period of 16 weeks. Dapsone stopped July 1976.
May 1979	PG occurred at site of trauma (left shin). Treatment : Clofazamine 200mg/daily x 5 weeks. Course : Was apparently healing on clofazamine. Stayed away.
August 1980	Ulcer of May 1979 had progressively deteriorated. Treatment : Dapsone 200mg/daily. Course : Healed completely over 8 weeks. Stopped Dapsone in December 1980.
January 1981	Returned with recurrence of PG (noted as "large areas of ulceration"). Treatment : Dapsone 200mg/daily (1 week supply prescribed). Course : Did not come for follow-up. Patient was last heard from in January 1987 when ulcers of January 1981 had eventually healed,

over several months, on no specific therapy and had not recurred up until that date.

COMMENT

A chronic, indolent course of 12 years before a diagnosis of PG was made and then a very favourable response to dapsone therapy within 16 weeks. Interesting to note the poor response to clofazamine when this was prescribed on one of his recurrences. The finding of leucocytoclastic vasculitis on skin histology, with no evidence of systemic vasculitis in an ulcer of such long standing is unusual.

CASE 37 : MR C.B. (Date of Birth 09/10/1916)

- June 1977 Injured left shin - ulcerated. Diagnosis : "Gangrenous infarct". Treatment : Surgical debridement and split skin graft. Course : "Sepsis" of donor and graft sites. Treatment : Antibiotics/ointments.
- September 1977 Non-healing ulcers of right shin and donor site (left thigh). Diagnosis : Pyoderma gangrenosum. Treatment : Clofazamine 300mg/daily. Course : No response after six weeks. Clofazamine stopped. Treatment : Methylprednisolone 48mg/daily. Response : Completely healed after 8 weeks. Methylprednisolone slowly tapered and eventually stopped in November 1978.
- March 1986 Last recorded hospital visit. Well. No PG. Further follow-up unavailable.
- COMMENT Pathergy almost certainly contributed to this patient's development of PG. His response to oral corticosteroids was prompt and complete. Tapering of corticosteroids took place extremely cautiously and no recurrence of PG occurred.

CASE 38 : MRS M.N. (Date of birth 01/01/1941)

- March 1977 Presented with extensive pyoderma gangrenosum. (Legs, arms, breast, scalp). Treatment : ACTH. Clofazamine. Partial response. Associated disease : None.
- December 1977 Further deterioration. Referred GSH. Treatment : Methylprednisolone 48mg/daily. Clofazamine 300mg/daily. INH prophylaxis.
- March 1978 Healed.

July 1978	Relapsed on Methylprednisolone 12mg/daily. Treatment : Methylprednisolone increased to 40mg/daily. Clofazamine 300mg/daily continued. Course : Healed.
October 1978	Discharged back to country hospital on tapering doses of corticosteroid and maintenance dose of Clofazamine 100mg/daily.
Follow - up	Established that patient died several months after discharge but exact nature of circumstances surrounding her death are unknown.
COMMENT	Good control for extensive disease achieved on therapy, but relapses with reduction of corticosteroid below 12mg/daily. Patient came from rural district, and follow-up was unfortunately not always satisfactory. An associated disease, despite in depth investigation, was never found.

CASE 39 : MR A.M. (Date of birth 07/05/1968)

April 1978	Referred with extensive pyoderma gangrenosum that had started in the genital area. No associated disorder was found (despite extensive investigations, which included bowel studies). Treatment : Prednisone 40mg/daily.
May 1978 - Dec 1978	Rampant disease. Clofazamine, dapsone, sulfapyridine, minocycline, azathioprine were added in sequence for periods varying between 4 and 6 weeks, for both therapeutic and steroid sparing effects, but all were uniformly unsuccessful.
27 December 1978	Patient died suddenly during dressing change. (Thought to be due to a cardiac arrest following on vasovagal stimulation during dressing changes).
COMMENT	Severe, extensive disease, which failed to respond to high dose corticosteroid. (40mg/daily in a 25kg boy). This is the only case of PG in the GSH series where oral corticosteroids in adequate doses failed to elicit a positive response. Despite fulminant extensive skin lesions (almost total body involvement at the end), no underlying systemic disease was found. Judging from the literature review, this degree of cutaneous involvement in PG is rare.

CASE 40 : MR M.B. (Date of birth 08/09/1954)

June 1988	Single superficial lesion of pyoderma gangrenosum of midback. (figure 6). Treatment : Prednisone 40mg/daily.
December 1988	Completely healed on tapering doses of prednisone.
February 1989	Weaned off prednisone.
April 1990	Pyoderma gangrenosum at lower end of previous lesion had re- curred. Treated himself at home. No improvement.
July 1990	Treatment : Minocycline 200mg/daily commenced. Course : Pro- gressive deterioration.
September 1990	Admitted for pulse Methylprednisolone 1G IVI/daily for 3 days (mi- nocycline stopped) then continued with oral prednisone 60mg/daily and Sulfasalazine 4G/daily. Lesion had begun to decrease in size and good healing had taken place when last seen. (15/10/1990). Sulfasala- zine was stopped as patient complained of intolerable headache.

COMMENT This patient's PG, clinically and histologically, bests fits the superfi-
cial, vegetative type of pyoderma gangrenosum described by Wilson-
Jones et al.⁴⁵

It remains to be seen whether the aggressive therapy i.e. pulse
methylprednisolone, results in permanent/prolonged remission. This
form of therapy was chosen in this patient because of the inac-
cessible site of the lesion for dressings (patient lived alone) and an in-
creasing depression as a result of the constant oozing from the site
which had adversely affected his working and social life. He may well
have cleared with consistent therapy (other than corticosteroids) had
the circumstances been ideal. In the Wilson-Jones series⁴⁵, healing
occurred without systemic corticosteroid therapy in all but three of
the twenty-five patients. Healing in the remaining patients took
place with local or intralesional corticosteroid, minocycline, tetracy-
cline or sulfa drugs.

CASE 41 : MISS M.A. (Date of birth 04/06/1958)

December 1975	Three year history of recurrent leg ulcers. Pyoderma gangrenosum di- agnosed. No associated disorder found. Treatment : Methylpredniso- lone 24mg/daily. Course : Healed slowly with occasional deterioration when failed to take oral corticosteroids.
March 1977	Healed completely.

April 1977 Weaned off corticosteroids.

April 1977 - Sep 1990 No further recurrence of pyoderma gangrenosum. Alive and healthy.

COMMENT This young woman responded to oral corticosteroids alone. The maintenance dose of Methylprednisolone for the greater part of the course was not more than 8mg/daily and deterioration only occurred when she stopped taking the medication altogether. With gradual weaning of the corticosteroid (after complete healing had taken place) remission has been maintained to date.

CASE 42 : MR N.S. (Date of birth 04/08/1928)

November 1974 Ulcer of left lower leg x 4 months (figure 17). Diagnosis : Pyoderma gangrenosum. No associated disease. Histology : Leucocytoclastic vasculitis. (no systemic involvement). Treatment : Tetracycline 2G/daily.

January 1975 Initial ulcer had healed but new lesion had developed at edge of the old lesion. Treatment : Tetracycline 2g/daily continued. Topical care.

February 1975 Ulcer "almost healed". Lost to follow-up.

COMMENT This is the only patient in the series where tetracycline alone was chosen for PG, with apparent initial success. It is interesting that a favourable response was obtained in a patient where leucocytoclastic vasculitis was demonstrated on histology of the cutaneous lesion.

CASE 43 : MR J.T. (Date of birth 00/00/1905)

January 1971 Admitted with extensive disease involving arms, chest, abdomen. Skin ulcers had started 2 years previously. No associated disorder. Treatment : Methylprednisolone 64mg/daily.

May 1971 Discharged with skin lesions "almost healed". Course complicated by development of diabetes mellitus which gradually resolved as the oral corticosteroid was tapered. Follow-up unobtainable.

COMMENT Patient spent almost 5 months in hospital with extensive disease. Patient is known to have remained well after discharge, but unfortunately his hospital record of follow-up visits has been destroyed. Extensive investigations revealed no underlying disease.

CASE 44 : MR T.P. (Date of birth 00/00/1939)

- September 1981 Referred re non-healing ulcers of legs. Diagnosis : Pyoderma gangrenosum. Treatment : Prednisone. Dapsone 100mg/daily.
- 1980 - Jan 1989 Followed up at country hospital. Episodes of deterioration (mainly when he stopped taking the medication).
- February 1989 Admitted to GSH with widespread deterioration. Treatment : Prednisone 80mg/daily. (Subsequently increased to 160mg/daily).
- Feb 1989 - Dec 1989 Prolonged hospital stay, due to recalcitrant disease, complicated by development of Insulin dependent diabetes mellitus and pulmonary tuberculosis. Medications added (in sequence) for therapeutic and steroid sparing effects were : Clofazamine, sulfasalazine, azathioprine, thalidomide. All of these failed to allow tapering of prednisone. Throughout hospital stay, no control of PG was ever attained.
- December 1989 DIED. (Cause of death - DIABETIC KETOACIDOSIS). Still had several areas of ulceration. Treatment at time of death : Prednisone 100mg/daily Azathioprine 100mg/daily, Thalidomide 200mg/daily. (The prednisone had been cautiously lowered just prior to his death, as the thalidomide which had been started 4 weeks prior to his death appeared to be having a positive effect. Unfortunately, he succumbed to the diabetic state when allowed home for a short period after an 11 month continuous hospital stay).

CASE 45 : MR G.T. (Date of birth 06/09/1944)

- August 1977 "Abscess" of left inguinal region incised and drained. Complained of haemoptysis - Mantoux - ulcerated to such a degree that grafting of the area was required. Repeated sputa for acid-fast bacilli (AFB) negative. Treatment : Antibiotics Course : Grafted area healed poorly.
- November 1977 Ongoing haemoptysis, loss of mass, fever. Skin lesions persisted. Diagnosis : Pulmonary Tuberculosis (TB)(positive sputum culture). Treatment : Rifampicin, Streptomycin, Isoniazid. Course : Responded favourably re TB but skin lesions persisted.
- February 1978 New cutaneous ulcers developed (lower limbs). Treatment : Antibiotics. Course : Healed poorly

September 1978	Diagnosis : Pyoderma gangrenosum. Treatment : Clofazamine 300mg/daily. Response : Healed poorly.
January 1979	Further deterioration. Treatment : Methylprednisolone 32mg/daily. Isoniazid prophylaxis. Response : Good.
Feb 1979 - Aug 1981	Intermittent flares of PG required increases of methylprednisolone from 12mg/daily to 48mg/daily (for short periods). Course : PG healed completely by August 1981.
September 1981	Recurrence of severe pulmonary TB. (despite isoniazid prophylaxis - although compliance with therapy was questioned). Treatment : Rifampicin, Ethambutol, Isoniazid. Maintenance methylprednisolone 8mg/daily.
January 1982	Failed to come for TB and PG follow-up.
April 1982	Lung disease flared. No PG present. Treatment : Anti - TB treatment re-introduced. Course : General condition deteriorated.
September 1982	Admitted to TB hospital. Extensive pulmonary disease.
October 1982	PG started to flare. Despite anti-TB therapy, died on 26/10/1982.

COMMENT *This patient's PG was associated with troublesome pulmonary tuberculosis. Tests of neutrophil function, prior to commencing corticosteroid therapy for PG, showed a neutrophil killing time of 0% (compared to 100% of the control). The chemotaxis and phagocytosis was apparently normal. An "ulcerating" mantoux indicated adequate cell-mediated immunity. Neutrophil defects in PG have been reported in the past⁶⁸⁻⁷⁰. Although drug resistance may have been a problem at the end, the overwhelming nature of the pulmonary disease indicated a breakdown in immune mechanisms (more likely humoral). Although PG was only diagnosed in 1978, the ulcerating Mantoux of 1 year previously and subsequent poor healing thereafter, indicates that it was probably an area of PG already at that stage of the disease course.*